Outcomes five years after primary lens implantation in children aged under two years with congenital cataract: Findings from the IoLunder2 UK and Ireland prospective inception cohort study

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Research in context

Evidence before this study

A systematic review of the evidence was undertaken when this study was co-designed with the British Isles Congenital Cataract Interest Group (BCCIG) in 2008. We searched PubMed, Scopus, Web of Science, and Embase for studies published before June 2008 with the terms ((“congenital cataract” OR “infantile cataract”) AND “Lens implantation, Intraocular”) OR ((“congenital cataract” OR “infantile cataract”) AND “surgery” AND (“randomised controlled trials” OR “cohort” or “longitudinal”)). There were no randomised controlled trials on intraocular lens (IoL) use in children aged under two years with congenital or infantile cataract. A single prospective cohort study of infants with unilateral congenital cataract undergoing surgery in the first 6 months of life reported, without adjusting for confounders, better visual outcome in 18 infants implanted with IOLs versus 23 children managed with contact lenses. The other studies reporting outcomes with and without IoLs comprised small case series (most with fewer than 20 children) and retrospective study designs. From this literature, meta-analyses was not possible due to study heterogeneity, however it appeared possible that visual outcomes following primary IOL implantation in children under two years old compared favorably to outcomes following conventional therapy.

A randomised controlled trial of IoLs versus conventional treatment in the subgroup of children aged ≤six months with unilateral cataract was published whilst our study was in progress. Findings comprised an increased risk of complications with IoL use without any visual benefit.

Added value of this study

The IoLunder2 population-based prospective inception cohort study shows no evidence of benefit, and risk of harm with IoLs in children aged two years and under, including those with bilateral cataract who represent the majority of the clinical population, and those at greatest risk of blindness.

Implications of all the available evidence

Collectively, the available data suggests that primary IoL implantation cannot be recommended as routine practice for children aged under two years old with congenital and infantile cataract. Where IoL implantation is being considered in this group of children, families and clinicians should be aware of the extant evidence concerning risks. Younger age at surgery remains the key prognostic factor for good vision, underscoring the importance of maintaining or instituting newborn / infant screening programmes to ensure early detection of cataract.

Introduction

Childhood visual disability profoundly impacts on physical, emotional and social development.[1,2] The need for life-time support and loss of productivity also confers societal financial burden.[2] Although rare, affecting between three to 10 per 10,000 children, congenital and infantile cataract is the leading cause of avoidable childhood blindness worldwide,[3] and a priority for international health programmes.[3] In the United Kingdom's Newborn and Infant Physical Examination programme, ocular examination occurs within 72 hours of birth, and again at six to eight weeks. This ensures prompt referral for treatment, the key to good visual outcomes.[3]

At birth, visual resolution is poor, with acuity of 1·0logMAR (**log**arithmic conversion of **M**inimum **A**ngle of visual **R**esolution), a level at which an adult would be considered as severely visually impaired. By five to seven years of age, acuity has improved tenfold driven by visual stimulation, reaching normal adult levels of 0·0logMAR.[4] Thus, visual rehabilitation to encourage this developmental trajectory in children rendered 'aphakic' (*without lens*) after conventional cataract surgery is as important as surgery itself.[5,6] Primary (i.e. concurrently with cataract surgery) implantation of an intraocular lens, or IoL, is routine in adult surgery but a recent innovation for managing the very different scenario in infancy.[7] Early adopters postulated improved visual outcomes, alongside protection against glaucoma, the key blinding iatrogenic complication.[7] IoL implantation was rapidly adopted internationally with the hope of these outcomes, but in the absence of robust supportive evidence.[7–11] By 2009, IoL implantation was undertaken routinely by most paediatric cataract surgeons, with loss of the clinical equipoise needed to proceed to a randomised controlled trial of this intervention in the UK.[7]

We investigated outcomes of congenital and infantile cataract surgery undertaken in the first two years of life, with and without primary IoL implantation, through IoLunder2, a prospective cohort study undertaken through the British Isles Congenital Cataract Interest Group (BCCIG).[12–14] Indicative early outcomes at one year following surgery, comprising absence of visual benefit with implantation in unilateral cataract, but possible visual benefit following

bilateral surgery, were previously reported.[15] We now report outcomes at five years following surgery, a stable and meaningful time for visual development, and by which time key post-operative complications are manifest.[4] We report outcomes overall, and compare those who underwent IoL implantation, and those who were potentially eligible for IoL implantation but were treated conventionally.

Methods

Ethics approval in the UK was granted by the Health Research Authority (Ref. 4295), and in the Republic of Ireland through institutional committees. Informed consent to collect and analyse data was obtained.

Case ascertainment and data collection

Details of case definition, ascertainment, and data collection have been reported.[15] Children aged two years and under undergoing surgery for congenital or infantile cataract, in the UK or Ireland, between 1st January 2009 and 31st December 2010 were eligible for inclusion. High levels of ascertainment were achieved through active surveillance through the BCCIG.[16] Data on potential predictors of outcome and confounders, agreed *a priori* by evidence based consensus (appendix S1A), were collected prospectively. Significant ocular comorbidity was defined as the presence of any of the following: complex persistent fetal vasculature, other ocular structural anomaly, severe microcornea (horizontal corneal diameter less than 9·5mm), or severe microphthalmos (axial length less than 16mm).[15] These abnormalities were agreed by clinical consensus as precluding IoL implantation.[7] Post-operative visual rehabilitation was assessed at one, three and five years following surgery. Type of, and carer reported concordance with refractive correction and prescribed amblyopia therapy were recorded.

Outcomes of interest at five years after surgery

Best corrected visual outcome was measured at least five years after surgery. Acuity was tested within a well-lit environment using a 4 metre logMAR notation test, or if necessary Cardiff,

Kays or Teller grating acuity cards. Where vision had to be assessed qualitatively, outcomes were assigned a logMAR score (appendix S1A).[17] Best achieved acuity measured during the six months following the five year post-operative milestone was used as the primary outcome measure. WHO thresholds were used to define visual impairment:[2,3] vision worse than 1·3logMAR is blindness, 1·01 to 1·3 severe visual impairment, 0·49 to 1·0 moderate visual impairment (i.e. the conventional minimum threshold for needing educational support such as large print texts), and 0·22 to 0·48 mild impairment (i.e. worse than the minimum UK threshold for driving).Standardised definitions were applied to the two most significant post-operative adverse outcomes, secondary glaucoma (using World Glaucoma Association taxonomy)[18] and visual axis opacity (VAO) (appendix S1A).[15]

Statistical analysis

Age at surgery was analysed as both a continuous and a categorical variable anchored in clinically relevant milestones.[15] Further details on study variables are provided (appendix S1A). Unilateral and bilateral cases were analysed separately. Multivariable linear and logistic regression, as appropriate, were used to model the association between primary IoL implantation and outcomes of interest restricted to those children without significant ocular anomaly (ie those meeting the consensus clinical eligibility criteria for IoL implantation).[7] Cases in which IoL implantation was undertaken, but was reversed perioperatively, were analysed within the IoL group according to intention-to-treat principles. Associations are reported with adjustment for known confounding factors.

Correlation between variables was investigated adhering to both the current conventional threshold of $p<0·05$ and the more stringent proposed threshold of $p<0·005$ for a statistically significant correlation.[19] Multivariable analysis, using backward stepwise regression, included the most clinically relevant factors and those variables significant at a 10% level in initial univariable analysis. If these variables were highly correlated, the more statistically significant factor was selected for inclusion in the multivariable analysis. We retained factors in the

multivariable model if they altered the odds ratio estimate by more than 10% or were independently associated at a 5% significance level. We compared model fit with and without two-way interaction terms. Data from both eyes of children with bilateral cataract were used with robust variance estimates to account for within-child correlation. Analyses were undertaken using Stata (SE V15·1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ALS, PMC and JSR had full access to all study data.

Results

Between January 1st 2009 and December 31st 2010, 256 of the 306 eligible children identified by the BCCIG were recruited. 12 children were lost to follow up, four through emigration. Overall 7/256 children (2·7%) died during the five year follow up period. The full five year follow up dataset is available for 92% (235) of the recruited cohort. 106 of these children are female, 40/92 (44%) children had unilateral cataract and 68/143 (46%) bilateral disease.

The sample for the current analyses of outcomes of IoL implantation compared to conventional treatment comprise the 158 children without significant co-existent ocular anomalies (figure 1). Socioeconomic and baseline clinical characteristics are described in table 1. Primary IoL implantation was undertaken in 88/158 children (56%). In two cases, IoL implantation was undertaken but reversed due to poor fit perioperatively. When compared to the aphake group, children who underwent IoL implantation were older at surgery, and a lower proportion lived in relative deprivation. Of the children who underwent IoL implantation 15/79 (19%) lived in areas within the most deprived IMD[20] quintile compared to 26/67 (39%) children in the aphake group, (95% confidence interval difference in proportions 4% - 35%). There was a positive univariable association between living in relative deprivation, and undergoing surgery outside a 'high volume' clinical centre (chi^2 $p<0·05$, appendix S2A).

Table 1. Baseline sociodemographics and clinical features, and clinical management details for children without significant ocular co-morbidity, n=158

	Bilateral cataract			Unilateral cataract		
	Aphake n=52 (104eyes)	**IoL n=50 (100eyes)**	**Total n=102 (204eyes)**	**Aphake n=18**	**IoL n=38**	**Total n=56**
Sex (female)	22 (42%)	23 (46%)	45 (44%)	9 (50%)	14 (37%)	23 (41%)
Ethnicity						
White British / Irish	*25 (54%)*	*33 (69%)*	*58 (62%)*	*9 (60%)*	*28 (78%)*	*37 (73%)*
Missing	*6*	*2*	*8*	*3*	*2*	*5*
Socioeconomic status						
Living in area of relative deprivation (lowest quintile of IMD)	*23 (46%)*	*13 (29%)**	*36 (38%)*	*3 (18%)*	*2 (6%)*	*5 (10%)*
Missing	*2*	*5*	*7*	*1*	*4*	*5*
Age at diagnosis in weeks	1 (0 - 72)	7 (0 - 97)	2 (0 – 97)	**0·6 (0 - 66)**	**19* (0 - 96)**	6 (0 – 96)
Age at surgery in months	**2 (0·6 – 17·1)**	**4·4 (0·9–23·7)***	3 (0·6– 23·7)	**1·7 (0·9–16·4)**	**7·7 (0·5–23·2)***	2·2 (0·5-23·2)
Aged 0- 4·35 weeks (eyes)	10 (10%)	5 (5%)	15 (7%)	3 (17%)	6 (16%)	9 (16%)
4·3 – 8·5 weeks	34 (33%)	18 (19%)	52 (26%)	8 (44%)	6 (16%)	14 (25%)
8·6 – 12·75 weeks	24 (23%)	8 (8%)	32 (16%)	4 (22%)	3 (8%)	7 (13%)
12·8 – 26 weeks	23 (22%)	25 (25%)	48 (24%)	1 (6%)	3 (8%)	4 (7%)
Over 26 weeks (6 months)	12 (12%)	43 (43%)	55 (27%)	2 (11%)	19 (50%)	21 (38%)
Time to second eye cataract surgery, days	7 (0 – 49)	7 (0-56)	7 (0 – 56)	-	-	-
Microphthalmia or microcornea	54 (*52%*)	57 (*57%*)	113 (*55%*)	7 (*39%*)	20 (*53%*)	27 (*48%*)
Persistent fetal vasculature	2 (*2%*)	0	2 (1%)	7 (*39%*)	9 (*24%*)	16 (*29%*)
Systemic disorder or neurodevelopmental impairment	15 (*29%*)	13 (*26%*)	28 (*27%*)	0	5 (*13%*)	5 (*9%*)
Perioperative management (eyes)						
Corneolimbal wound + capsulorhexis + PPC + AV	94 (*90%*)	89 (*89%*)	183 (*90%*)	17 (*94%*)	36 (*95%*)	53 (*95%*)
Implantation of hydrophobic acrylic implant	-	98 (*98%*)	-	-	38 (*100%*)	-
Periocular / intraocular steroids on completion	92 (*88%*)	96 (*96%*)	188 (*92%*)	15 (*83%*)	36 (*95%*)	51 (*91%*)
Intensive regimen of topical steroids post op	35 (*34%*)	49 (*49%*)	84 (*41%*)	4 (*22%*)	15 (*40%*)	19 (*34%*)
Post operative visual rehabilitation						
Contact lenses +/- glasses	17 (33%)	5 (10%)*	22 (22%)	6 (33%)	0*	6 (11%)
Glasses only	30 (58%)	43 (86%)	73 (72%)	8 (44%)	0	8 (14%)
Any occlusion / penalisation therapy	2 (4%)	6 (12%)	8 (8%)	16 (89%)	36 (95%)	52 (93%)
Good overall concordance with occlusion / penalisation	0/2	4/6 (67%)	4/8 (50%)	10/16 (63%)	21/36 (58%)	31/52 (60%)

All data available for full sample unless otherwise stated. Data are *n* children (%) and median (range) unless otherwise stated. Children may have more than one ocular morbidity, perioperative management type, or postop visual rehabilitation type, so totals may>100%

IMD: Index of Multiple Deprivation, PPC= primary posterior capsulotomy, AVity=anterior vitrectomy

*Statistically significant (p<0·01) difference aphakia versus IoL (highlighted in bold)

Visual outcome

Vision was measured using crowded logMAR notation at 4m in 91/102 (89%) children with bilateral disease (seven children other quantitative tests, four qualitative) and 51/56 (91%) children with unilateral cataract (one other quantitative tests, four qualitative).

Visual outcomes and associated factors in bilateral cataract

Five years after surgery, with both eyes open, the median best corrected acuity was 0·34logMAR (mild visual impairment), ranging from 0·06 (unimpaired), to 1·0 (severe impairment), with an interquartile range (IQR) of 0·2 (threshold for driving vision in the UK) to 0·54 (moderate impairment). Overall median uniocular visual outcome was 0·5logMAR (figure 2), 0·6 (IQR 0·4 to 0·9, range 0 – 3) in the aphake group and 0·4 (IQR 0·2 – 0·7, range 0-3) for children in the IoL group. Age at cataract surgery was the only modifiable independent predictor of visual outcome following bilateral cataract surgery in this subsample of children with no other significant ocular comorbidity. A two line difference in visual outcome has been accepted as a clinically meaningful outcome (ie adjusted coefficient of ≥0·2 or ≤-0·2).[6,21] When compared to surgery in the first month of life, there was a significant association between worse outcomes and surgery during the second (adj coeff 0·19, 95% CI 0 to 0·4, p=0·05) or third month (adj coeff 0·37, 95% CI 0·1 – 0·7), p=0·01). However, surgery during the third month of life was not significantly associated with worse outcome compared to the second month of life (contrast of marginal linear predictions 0·2, 96% CI -0·1 to 0·5, p=0·2). IoL implantation was not an independent predictor of better visual outcome (coefficient adjusted for confounders of age, microphthalmos / microcornea, and systemic abnormalities: -0·1, 95% CI -0·5 to 0·3, p=0·48).

Visual outcomes and associated factors in unilateral cataract

For children with unilateral cataract, overall median outcome in the operated eye was 0·7logMAR, ranging from 0 to 3·0 (unable to perceive light in the operated eye), IQR 0·3 (mild impairment) to 1·3 (within the WHO definition of blindness). Median outcome was 1·0 (IQR 0·5

to 1·4, range 0·1 – 3) in the aphake group and 0·4 (IQR 0·3 – 0·7, range 0-3) for children in the IoL group.

Good overall concordance with post-operative occlusion therapy versus poor concordance (including stopping occlusion due to poor concordance) was the only statistically significant modifiable predictor of better visual outcomes for operated eyes in children with unilateral cataract (table 2). IoL implantation was not an independent predictor of better visual outcome (coefficient adjusted for age and concordance with occlusion: -0·3, 95% CI -0·6 to 0·2, p=0·36).

Table 2: Factors independently associated with visual outcome in (a)bilateral and (b)unilateral cataract+

a. Bilateral cataract, (n=199 eyes, 100 children included in model)

	Adjusted coefficient (95% CI)	p value
Mild microphthalmia or microcornea	0·14 (-0·0 to 0·3)	0·14
Post-operative glaucoma	0·28 (-0·0 to 0·7)	0·12
Age at surgery (categorised)		
Baseline (0 – 4·3 weeks)	-	-
4·4 – 8·5 weeks	0·19 (0 to 0·4)	0·05
8·6 – 12·75 weeks	0·37 (0·1 to 0·7)	0·01*
12·8 – 26 weeks	0·13 (-0·1 to 0·7)	0·24
Aged over 26 weeks (6 months)	0·14 (-0·0 to	0·55
Neurodevelopmental disorder / impairment	0·39 (0·1 to 0·7)	0·01*

Adjusted coefficient for association of primary IoL implantation with visual outcome: : -0·1, 95% CI -0·5 to 0·3, p=0·48

b. Unilateral cataract (n=49 children included in model)

	Adjusted coefficient (95% CI)**	p value
Good overall concordance / never occluded (versus poor concordance / failed occlusion	-1·2 (-1·9 to -0·6)	<0·01*
Age at surgery (categorised)		
Baseline (0 – 4·3 · weeks)	-	-
4·4 – 8·5 weeks	0·12 (-0·4 to 0·6)	0·61
8·6– 12·5 weeks	0·28 (-0·7 to 0·1)	0·10
12·6 – 26 weeks	-0·23 (-0·9 to 0·4)	0·56
Over 26 weeks (6 months)	-0·08 (-0·6 to 0·4)	0·72

Adjusted coefficient for association of primary IoL implantation with visual outcome: -0·3, 95% CI -0·6 to 0·2, p=0·36

+ **(multivariable modelling, within-child clustering for bilateral cases, coefficient in logMAR units, negative coefficient better vision, positive coefficient worse vision)**

*Statistically significant association

**Including adjustment for diagnosis of neurodevelopmental disorder / impairment

Glaucoma

Secondary glaucoma was diagnosed in 22/260 eyes, or 19/156 children, (12%), comprising 14 children with bilateral, and five with unilateral cataract (table 3). Glaucoma-related adverse events[18] were diagnosed in 55/260 eyes (21%).

Bilateral cataract

Median time to glaucoma diagnosis was 3·6months (3·1m aphake group, 4·6m IoL group) ranging from 0·5m - 23m. Eight children with bilateral cataract underwent surgery for glaucoma, with a median number of two procedures per eye (range zero to four).

Unilateral cataract

Median time to glaucoma diagnosis was 1·8months ranging from 1·0m – 3·4m. Four children underwent glaucoma surgery (median number procedures one, range zero - seven). No child who underwent IoL implantation for unilateral cataract developed glaucoma, and 8/30 (21%) developed glaucoma-related adverse events (table 3).

Factors associated with risk of glaucoma

For children with both bilateral and unilateral cataract, increasing age at primary surgery was protective against glaucoma. IoL implantation was not protective for children with bilateral (OR 0·5, 95% CI 0·1 – 1·8, p=0·28) following adjustment for confounders. For children with unilateral cataract, higher socioeconomic status (independent of ethnicity) was associated with lower odds of developing glaucoma (table 4).

Visual axis opacity (VAO)

The most common adverse event was visual axis opacity requiring re-operation (table 3). All children underwent re-operation under general anaesthetic. For 50 of the 54 eyes (93%) affected by VAO, the first re-operation for VAO occurred within a year of primary surgery. IoL implantation for both bilateral and unilateral cataract was independently associated with an at least five times higher odds (and 95% lower limit odds ratio of >2) of requiring reoperation for VAO (table 4). For children with unilateral cataract, an intensive regimen of post-operative

topical corticosteroids (ie given at least two hourly for the first week with night time steroid ointment, compared to less frequent use) were associated with lower odds of VAO treatment at a 5% significance level.

Table 3: Adverse Outcomes

	Bilateral cataract			Unilateral cataract		
	Aphake n=104 eyes	**IoL n=100 eyes**	**Total n=204 eyes**	**Aphake n=18**	**IoL n=38**	**Total n=56**
Glaucoma-related adverse events						
None	77 (74%)	88 (88%)	165 (81%)	10 (56%)	30 (79%)	40 (71%)
Glaucoma	12 (12%)	5 (5%)	17 (8%)	5 (28%)	0	5 (8%)
Persistent ocular hypertension	11 (11%)	5 (5%)	16 (8%)	3 (17%)	4 (11%)	7 (13%)
Transient ocular hypertension	1 (1%)	0	1 (<1%)	0	3 (8%)	3 (5%)
Pupil block related	3 (3%)	2 (2%)	5 (2%)	0	1 (3%)	1 (2%)
Visual axis opacity (eyes)	10 (10%)	27 (27%)	37 (18%)	2 (11%)	15 (40%)	17 (30%)
Other (eyes)						
Retinal detachment	0	0	0	1 (6%)	1 (3%)	2* 4%
Endophthalmitis following primary surgery	0	0	0	0	0	0

* all eyes had pre-existing persistent fetal vasculature

Table 4: Factors independently associated with the adverse outcomes of glaucoma and visual axis opacity on multivariate analysis

	Bilateral		**Unilateral**	
Factors associated with risk of **GLAUCOMA**	Adj odds ratio (OR)	p	Adj OR*	p
Increasing age at surgery (weeks)	0·90 (0·85 to 0·96)	<0·01	0·91 (0·84 to 0·98)	<0·01
Increasing pre-operative axial length (mm)	0·82 (0·69 to 0·97)	0·03		
Higher socioeconomic status of family residence (ie living in less deprived IMD quintile)			0·25 (0·07 to 0·97)	0·04

	Bilateral		**Unilateral**	
Factors associated with risk of **VISUAL AXIS OPACITY**	Adj OR	p	Adj OR**	p
IoL implantation	5·94 (2·14 to 16·47)	<0·01	20·15 (3·01 to 134)	<0·01
Increasing age at surgery in weeks	0·96 (0·93 to 0·99)	0·01	0·96 (0·94 to 0·99)	<0·01
Intense post-operative topical steroid			0·15 (0·09 to 0·80)	0·03

*With adjustment for ethnicity, and persistent fetal vasculature

**With adjustment for persistent fetal vasculature

Discussion

From this first national cohort study of children aged under two years undergoing surgery for congenital or infantile cataract IoLs, we report that there is no evidence that IoLs are associated with better visual outcomes at five years after surgery in either bilateral or unilateral disease. There is no evidence that their use is associated with a reduced risk of secondary post-operative glaucoma following bilateral cataract surgery. IoL implantation did however confer a significantly increased risk of requiring further surgery under general anaesthetic, typically within the first post-operative year.

The value, and limitations, of 'Real-world' data in providing evidence on outcomes is increasingly recognised. We report a carefully conducted prospective cohort study comparing primary IoL implantation with established treatment (aphakic correction with contact lenses and or glasses) for children who would, by expert consensus, have been eligible for implantation, in which all potential confounders (previously reported or postulated) were accounted for in the analysis. Nevertheless, the possibility remains of residual confounding by unknown or unmeasured factors, just as it pertains to underpowered randomised controlled trials (RCTs). It is therefore notable that after our study started, an RCT in a subgroup of the whole population of interest, but in similar health care setting, reported similar findings with respect to absence of benefit and increased risk of complications with IoL use.[21]

We conducted IoLunder2 at a time when an RCT of IoL implantation was not possible due to the widespread adoption of IoLs (ie a lack of equipoise amongst clinicians) in the UK.[7] In this context, the strength of the study is that it draws on a nationally representative cohort, managed across a harmonised clinical research network, with evidence-based consensus-agreed clinical definitions, limiting the impact of selection or measurement biases. Whilst overall attrition was low, attrition rates were higher for children treated conventionally. For those with bilateral disease, in whom differential attrition may be attributable to differences in child mortality, higher prevalence of co-existent systemic abnormalities may have resulted in worse visual outcome in

the aphake group. However, reported associations between IoL implantation and visual outcome were adjusted for the presence of such abnormalities, limiting the impact of attrition bias. The families of 50 children eligible for inclusion within IoLunder2 did not consent to participation at the outset, so we have been unable to examine the impact of their non-inclusion. Detailed standardised data on birth history, biometric, peri-operative and systemic status enabled a rigorous investigation of the role of known potential confounders. Restriction of our analysis to the subsample of children without significant ocular co-morbidities (equivalent to 'matching'), also reduces the impact of unknown confounders on analyses.

It is possible that, for children with unilateral cataract in IoLunder2, the lack of a statistically significant association between IoLs and visual outcome may be due to insufficient power to interrogate outcomes. It is worth noting that no visual benefit of IoLs for children with unilateral cataract aged under seven months at surgery was reported in the North American RCT of primary IoL implantation versus aphakia (the Infant Aphakia Treatment Study, IATS).[21] No child within the IoLunder2 unilateral IoL group developed glaucoma, although 21% developed a glaucoma-related adverse event.[18] IATS similarly found no evidence of protection against glaucoma with primary IoLs.[22] IATS findings cannot offer insight into outcomes in either older infants or those with bilateral disease, i.e. the majority of affected children and those at most risk of cataract related blindness. A recently published RCT of primary IoLs in children aged under 2 years with bilateral cataract in India (single surgeon) unfortunately lacked sufficient power to determine difference in treatment effects, and its generalisability is limited by poor uptake of contact lens correction (2/25 children, 8%) and lack of reporting on the use of aphakic glasses.[23] Therefore it is important that IoLunder2 now demonstrates no evidence of a statically significant association of visual benefit with IoL implantation.

Ocular co-morbidity, a common finding in children undergoing cataract surgery in the UK, and an indicator of congenital rather than infantile or developmental disease, does not preclude visual benefit from treatment.[9,13–15] The necessary restriction of our analysis to children potentially

eligible for IoL implantation may have resulted in a greater proportion of children with infantile versus congenital disease relative to other population based studies.[5,8-10,14] This may explain the absence of a unidirectional association between increasing age at surgery and visual outcome, although this may also be explained by insufficient power due to small subgroup sample sizes. Our finding of an increased risk of reoperation for visual axis opacity following IoL implantation due to intraocular proliferation of remnant lens epithelial cells or inflammatory cells are similar to those reported by IATS.[22] There is emerging evidence on the adverse impact of repeated exposure to general anaesthetic on a child's global development,[24] with a recent FDA report recommending caution with the use of anaesthesia in children aged under three years.[25] This is of particular importance in this group of children: 2·7% of IoLunder2 children died during the five year follow up period, indicative of the complex multi-system disorders which coexist with childhood ocular anomalies.[13] IoLunder2 findings show no visual benefit and no protection against glaucoma, leading to the conclusion that IoL implantation in children under two years old with congenital or infantile cataract, rather than continuing as routine practice, should be undertaken with caution and full knowledge by both surgeon and family of the potential adverse outcome.

Younger age at surgery is the key modifiable predictor of outcome for children with congenital and infantile cataract. For children with bilateral cataract, there is a four logMAR line worsening of vision with surgery in the third month of life ($p<0·01$) versus the first month of life. Early surgery is particularly important for visual outcomes in truly congenital disease, to enable the early stimulus-dependent connections formed by the visual system during the critical neurodevelopmental window.[26] This window 'closes' at some point during early infancy.[26] IoLunder2 findings evidence the impact and importance of the continued inclusion of the ocular examination in the UK's National Screening Committee's Newborn and Infant Physical Examination (NIPE) Programme, and similar initiatives elsewhere. There is, however, a reduction in glaucoma risk with each additional week of age at surgery. The association of

younger age at surgery with both better vision, and increased rate of secondary glaucoma within IoLunder2 has been previously described from a UK population based cohort who underwent surgery 20 years ago,[12,14] and other prior work.[5,8,9] Prompt diagnosis affords the family the time they need to be counselled on the delicate balance between post-operative glaucoma and visual outcome with regards to the timing of surgery.

A key 'tipping point' in the trajectory of the diffusion of any new surgical technology is the adoption by a few influential practitioners who act as ambassadors, facilitating more rapid uptake amongst the majority.[27] In this regard, the findings of difference of distribution of socioeconomic status (based on area of residence) between those who underwent IoL implantation versus conventional surgery is intriguing. Within the broader literature on predictors of outcome following adult non-ophthalmic surgery, relative socioeconomic deprivation has been reported as a predictor of whether individuals undergo surgery and of poorer outcomes following surgery,[28] but not adoption of novel surgical interventions. An explanation for our findings may lie in the negative association between living in an area of relative deprivation and undergoing surgery in a 'high volume' clinical centre, and the higher use of IoLs within these high volume centres (appendix S1A). A thorough exploration of these associations, and the impact of patient choice versus patient location, are beyond the scope of IoLunder2. Nevertheless, surgical communities should be aware of this potential variation in the implementation of new therapies. IoLunder2 findings also suggest a higher odds of post-operative glaucoma following surgery for unilateral cataract for children living in relative deprivation. Although the aetiogenesis of such an association is unclear, this socioeconomic inequality of disease risk is consistent with other early life health disorders.[29]

The ethical, methodological and logistic challenges of randomised controlled trials of rare diseases can be insurmountable. In this landscape, perceived need and optimism by can lead to the rapid adoption of medical innovation by practitioners hopeful of improved outcomes, with loss of the clinical equipoise needed to undertake a randomised trial. The drivers of the

widespread adoption of IoL implantation in congenital and infantile cataract surgery included the desire for improved outcomes, and potential limitations of aphakic contact lenses, including the need for frequent replacement, specialist optician support and a clean water supply for safe use. Our findings on the potential risk of harm conferred by primary IoL implantation through increased need for repeated general anaesthetics, without evidence of benefit, when married to similar evidence from a recent RCT, are sufficiently strong as to challenge whether the equipoise necessary for further trials exists. We suggest that parents of young children with cataract, their clinicians and research ethics committees will require compelling new evidence of benefit and reassurance about potential harms – for example from developments in lens design or surgical technique, to enable future trials to be conducted. IoLunder2, supported by a multicentre collaborative clinical network which also forms a translational matrix for study findings. It demonstrates the value of a carefully conducted prospective cohort study in assessing the risks and benefits of a novel intervention for a rare disease when an RCT cannot be conducted, and thereby lead to changes in clinical policy and practice.

Declaration of interests

The authors declared no conflicts of interest

Author contributions

All authors contributed equally to study conceptualisation and design, data acquisition and analysis, interpretation, manuscript drafting and revision. All authors give final approval of the version to be published. ALS and JSR agree to be accountable for all aspects of the work.

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