• Clinical Research •

Timing and approaches in congenital cataract surgery: a four-year, two-layer randomized controlled trial

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Abstract

• AIM: To compare visual prognoses and postoperative adverse events of congenital cataract surgery performed at different times and using different surgical approaches.

• METHODS: In this prospective, randomized controlled trial, we recruited congenital cataract patients aged 3mo or younger before cataract surgery. Sixty-one eligible patients were randomly assigned to two groups according to surgical timing: a 3-month-old group and a 6-month-old group. Each eye underwent one of three randomly assigned surgical procedures, as follows: surgery A, lens aspiration (I/A); surgery B, lens aspiration with posterior continuous curvilinear capsulorhexis (I/A+PCCC); and surgery C, lens aspiration with posterior continuous curvilinear capsulorhexis and anterior vitrectomy (I/A+PCCC+A-Vit). The long-term best-corrected visual acuity (BCVA) and the incidence of complications in the different groups were compared and analyzed.

• RESULTS: A total of 57 participants (114 eyes) with a mean follow-up period of 48.7mo were included in the final analysis. The overall logMAR BCVA in the 6-month-old group was better than that in the 3-month-old group (0.81±0.28 *vs* 0.96±0.30; *P*=0.02). The overall logMAR BCVA scores in the surgery B group were lower than the scores in the A and C groups (A: 0.80±0.29, B: 1.02±0.28, and C: 0.84±0.28; *P*=0.007). A multivariate linear regression revealed no significant relationships between the incidence of complications and long-term BCVA.

• CONCLUSION: It might be safer and more beneficial for bilateral total congenital cataract patients to undergo surgery at 6mo of age than 3mo. Moreover, with rigorous follow-up and timely intervention, the postoperative complications in these patients are treatable and do not compromise visual outcomes.

• **KEYWORDS:** pediatric cataract surgery; postoperative complications; long-term visual function

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INTRODUCTION

Fighting childhood blindness from congenital cataracts is a priority of Vision 2020: The Right to Sight, a global initiative aimed at reducing the world's burden of avoidable blindness[1]. Congenital cataracts occur when visual development is in its sensitive and critical stages[2]; therefore, applying inappropriate surgical interventions in children may not only fail to restore visual function but also cause irreversible effects on eyeball development[3-4].

Debate over the optimal timing for congenital cataract surgery persists, which presents challenges for pediatric ophthalmologists[5]. Several early studies suggested that delaying cataract surgery in infants increases the risk of developing resistance to amblyopia treatment and decreases potential visual functions[6-8]. As a result, pediatric surgeons sought to complete lens-removal surgery during the very early stages of life[9-10]. However, recent studies have demonstrated that early surgery is associated with a greater prevalence of secondary membrane formation and the development of aphakic glaucoma[5,11-12]. Additionally, delayed presentation to the hospital and late surgical treatment are very common in China, which has no national screening or follow-up system for infants, and the surgical information of these patients always remains unclear[13]. Therefore, making decisions with regard for surgical timing alone may be insufficient to substantially and efficiently improve the long-term visual outcome in infants with congenital cataracts[14].

Furthermore, selecting the surgical approach for congenital cataracts is challenging for ophthalmologists. A major postoperative problem is the formation of secondary cataracts. Because the posterior capsule and the anterior vitreous face act as scaffolds for the proliferation of lens epithelial cells (LECs), performing lens aspiration with posterior continuous curvilinear capsulorhexis (I/A+PCCC) or lens aspiration with posterior continuous curvilinear capsulorhexis and anterior vitrectomy (I/A+PCCC+A-Vit) in infants may interrupt the development of visual axis opacification and consequently reduce the rate of secondary cataracts[15-17]. However, excessive operations can disrupt normal ocular anatomical relationships in addition to the blood-aqueous barrier, thereby increasing the risk of postoperative complications, including serious inflammation, intraocular hypertension and secondary glaucoma[15,18], which may subsequently impair eyeball development and visual rehabilitation. Therefore, when selecting the type of surgical procedure to be used, tradeoffs should be carefully considered before treatment decisions are made[19].

In this trial, we aimed to compare the differences in visual prognoses and postoperative adverse events between surgeries performed at two different times (at 3mo *vs* 6mo of age) using three surgical approaches (I/A, I/A+PCCC, and I/A+PCCC+A-Vit). We sought to obtain new insights into the optimal intervention strategies to use in patients with bilateral total congenital cataracts.

SUBJECTS AND METHODS

Patients A total of 65 children registered the Childhood Cataract Program of the Chinese Ministry of Health (CCPMOH)[20] were recruited between January 2010 and March 2011 from Zhongshan Ophthalmic Center[21], one of the largest eye hospitals in China.

Ethics Approval The research protocol was approved by the Institutional Review Board/Ethics Committee of Sun Yat-sen University (Guangzhou, China). Informed written consent was obtained from at least one family member of each participating patient, and the tenets of the Declaration of Helsinki were followed throughout this study. This trial was registered with the Clinical Research Internal Management System of Zhongshan Ophthalmic Center and ClinicalTrials.gov (NCT02581046).

Inclusion and Exclusion Criteria The inclusion criteria were 1) gestational age at birth>37wk, 2) ≤3mo of age, 3) diagnosis of bilateral "total" cataracts (*i.e.* dense opacity covering the entire lens)[22], 4) informed written consent from at least one family member.

The exclusion criteria were the presence of any of the following: 1) >3mo of age; 2) history of glaucoma, ocular trauma, corneal disorders, persistent hyperplastic primary vitreous, rubella, Lowe syndrome, or capsular fibrosis or the presence of any coexisting ocular, systemic or neurological diseases; 3) absence of normal dilation of the pupils; 4) inability to complete follow-up for any reason.

Randomization and Masking Participants were assigned using a simple randomization (1:1) procedure to the 3-month-old surgical group or the 6-month-old surgical group[23]. Surgical methods (I/A, I/A+PCCC, I/A+PCCC+A-Vit) were randomized in each eye of the participants. The randomization codes were generated using a random number generating program (Random number generator tools, version 1.4, Duote Co., Wuhu, China). Written allocation assignments were sealed in individual opaque envelopes that were marked with only study identification numbers. Regular ocular examinations and analyses were performed by investigators and clinical staff, both of whom were masked to group allocation. The participants, the study personnel in charge of randomization and the pediatric ophthalmic surgeons could not be masked because the intervention required their overt participation.

Intraoperative and Postoperative Procedures After randomization, participants accordingly underwent bilateral cataract surgery at 3 or 6mo of age ±10d by two experienced cataract surgeons (Liu YZ and Chen WR). The patients randomized to surgery at age 6mo were administered with compound tropicamide eye drops twice a day to increase the light into fundus and closely followed up for the three months after randomization prior to surgery. General anesthesia was administered prior to surgery. After a temporal clear corneal incision was made, a DuoVisc and a soft-shell technique were used to reform and stabilize the anterior chamber and protect the corneal endothelium. A 5.5-6.0 mm central continuous curvilinear capsulorhexis was created using a bent 26-gauge disposable needle. Hydro-dissection was performed using a balanced salt solution, and a standard phacoemulsification was performed to completely remove the lens. In the surgery A group (I/A), the surgery was completed during this step. In the surgery B group (I/A+PCCC), posterior capsulorhexis was performed using a cystotomy cannula. The surgery C group underwent both procedures in addition to an anterior vitrectomy (I/A+PCCC+A-Vit).

The postoperative topical therapy included the administration of 0.3% tobramycin and 0.1% dexamethasone eye drops (Tobradex, Alcon Laboratories, Inc., Texas, USA) four times per day and 0.3% tobramycin and 0.1% dexamethasone eye ointment (Tobradex, Alcon Laboratories, Inc., Texas, USA) every night for one month.

Follow-up Protocol and Assessment Methods Follow-up appointments were scheduled according to our previously described protocol[24]. All of the patients returned for 12 scheduled follow-up visits at 1wk, 1, 3, 6, 9mo, 1, 1.5, 2, 2.5, 3, 3.5 and 4y after surgery. Specifically, an orthoptic assessment and intraocular pressure (IOP) measurement using a Tono-

pen tonometer (Reichert Inc., Seefeld, Germany) were conducted[25-26]. Concurrently, the ocular anterior segment was examined using pupil dilation with slit-lamp photography (BX 900H Photo Slit Lamp, Haag-Streit AG, Switzerland) at every follow-up visit. Nd:YAG laser capsulotomy was performed once the visual axis appeared opaque, and postoperative IOP and inflammation were recorded. All Nd:YAG laser capsulotomies were performed by using a Zeiss Visulas Yag II Laser System (Carl ZeissMeditec, Germany), and a contact lens with a coupling agent was applied to the eye to improve focusing of the laser beam. The general anesthesia process was applied for the uncooperative children.

For consistency, a complete set of Teller visual acuity (VA) cards (Stereo Optical Company, Inc., IL, USA) was used to measure the monocular and binocular best-corrected visual acuity (BCVA) with spectacles throughout the follow-up[27-28]. The set consisted of 15 cards with grating ranging in spatial frequency from 0.32 cycles/cm to 38 cycles/cm in half-octave steps as well as a low vision card and a blank gray card. The infant was assessed using the standard procedure of the operation manual[29-30]. All the VA tests were conducted by a single experienced pediatric optometrist (Li XY) to minimize bias during the infant visual examinations. Monofocal spectacles were used to accommodate aphakic eyes and amblyopia treatment. The first spectacle prescriptions were assigned to the participants at 1wk after surgery. The prescription changed when the variance of spherical power was more than 2 diopters or the variance of astigmatic power was more than 1 diopter. All the changes in spectacles were decided by experienced specialists who were masked to group assignment. All the included patients have not been implanted with intraocular lens during follow-up process.

Definition of Adverse Events Glaucoma was defined as IOP>21 mm Hg with 1 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, which was defined as an increase ≥0.2 in the cup-to-disc ratio; and 4) the use of a surgical procedure to lower IOP[31].

Glaucoma suspect was defined as either 1) two consecutive IOP measurements above 21 mm Hg on different dates after topical corticosteroids had been discontinued without any of the anatomical changes listed above or 2) the use of glaucoma medications to control IOP without any of the anatomical changes listed above[31].

Abnormal high IOP was defined as IOP>21 mm Hg[25].

Severe posterior capsular opacification (PCO) was defined as LEC proliferation extending into the pupillary space and covering the visual axis. Nd:YAG laser capsulotomy was applied in a timely manner[32].

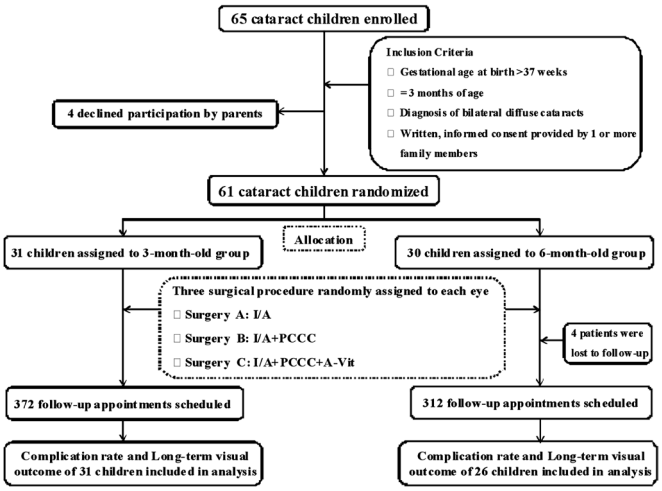

Figure 1 Flow chart of patient selection and follow-up protocols
I/A: Lens aspiration; I/A+PCCC: Lens aspiration with posterior continuous curvilinear capsulorhexis; I/A+PCCC+A-Vit: Lens aspiration with posterior continuous curvilinear capsulorhexis and anterior vitrectomy.

Statistical Analysis We used the reported long-term BCVA (3-month BCVA: 0.52±0.17; 6-month BCVA: 0.61±0.22) as described in several previous studies as our reference rate, and our sample size was calculated to detect a 10% difference in visual outcomes[5,7-8]. We calculated that a sample size of 63 participants (126 eyes) (assuming a 1:1 allocation ratio with 366 appointments in each group) would be required to achieve 80% power at a 0.05 level of significance.

Demographic and clinical information were recorded at baseline. Study population characteristics are presented as mean±standard deviation. Based on an analysis of observed and expected frequencies, Chi-square tests or Fisher's exact tests were used to examine the impact of the surgical method and its timing on postoperative complications. Kruskal-Wallis tests were used to compare the logMAR monocular BCVA between treatment groups. Because of the nested structure of the eyes, a generalized estimating equation was integrated into the multivariate linear regression to explore the relationship between long-term monocular BCVA and the incidence of complications[33]. All statistical tests were two-tailed, and a *P*-value below 0.05 was considered statistically significant. The statistical package SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all of the statistical analyses.

RESULTS

Study Population Between February, 2010 and March, 2011, we recruited 65 children with bilateral total congenital cataracts (Figure 1). After screening, 4 children were excluded because their parents declined participation. The remaining 61 participants were randomly assigned to the following surgical timing groups: 3mo (*n*=31) and 6mo (*n*=30). Four patients in the 6-month-old group were lost to follow-up after surgery. The remaining 57 participants completed their follow-

up appointments during the 4y following surgery as initially scheduled, including 372 appointments in the 3-month-old group and 312 appointments in the 6-month-old group. A total of 605 (88%) out of 684 expected follow-up visits were completed. Table 1 shows the baseline characteristics of each group, and no significant differences were observed between the groups.

Best-Corrected Visual Acuity The preoperative BCVA of all of the participants was light perceptions or worse, as measured by Teller VA cards at baseline prior to surgery (within 1d after randomization). The preoperative BCVA results demonstrated no significant difference between the groups (all groups exhibited poor results). Postoperatively, a total of 24 patients (48 eyes) in the 3-month-old group and 20 patients (40 eyes) in the 6-month-old group underwent BCVA testing using Teller VA cards by a single experienced pediatric optometrist (Li XY) to minimize bias. The age of the participants at the last VA test was 48.72±3.24mo (range, 42 to 54mo), and there was no significant difference in the age of the last VA test between the 3-month-old and 6-month-old groups and among all of the subgroups. The mean logMAR BCVA of the examined participants was 0.89±0.30.

As is shown in Figure 2, the overall logMAR BCVA in the 6-month-old group was better than that in the 3-month-old group (3mo, 0.96±0.30; 6mo, 0.81±0.28; *P*=0.02), and in each surgical procedure subgroup, the visual outcomes were better in the 6-month-old group (3A *vs* 6A: 0.87±0.26 *vs* 0.73±0.31, *P*=0.234; 3B *vs* 6B: 1.13±0.30 *vs* 0.89±0.20, *P*=0.005; 3C *vs* 6C: 0.86±0.25 *vs* 0.81±0.32, *P*=0.961). The outcomes in the best BCVA subgroup within the 3-month-old group were not significantly different from the outcomes in the worst BCVA subgroup within the 6-month-old group (3C *vs* 6B: 0.86±0.25 *vs* 0.89±0.20, *P*=0.724).

As shown in Figure 3, the overall logMAR BCVA scores in the B group were lower than the scores in the A and C groups (A: 0.80±0.29, B: 1.02±0.28, and C: 0.84±0.28, *P*=0.007; A *vs* B, *P*=0.009; B *vs* C, *P*=0.050), and within each surgical timing subgroup, the visual outcomes in the B group were the worst (3A: 0.87±0.26, 3B: 1.13±0.30, 3C: 0.86±0.25, *P*=0.003; 3A *vs* 3B, *P*=0.013; 3B *vs* 3C, *P*=0.007; 6A: 0.73±0.31, 6B: 0.89±0.20, 6C: 0.81±0.32, *P*=0.398; 6A *vs* 6B, *P*=0.316; 6B *vs* 6C, *P*=0.592).

Postoperative Complications The majority of adverse events occurred within the first six months following surgery (62/95, 65.3%), and very few complications occurred during the mid-term period, from 6mo to 2y (9/95, 9.5%). Furthermore, severe PCO (33/95, 34.7%) and abnormally high IOP (60/95, 63.1%) were detected for up to 6mo after surgery and were the most common adverse events in each postoperative period (Figure 4). The two (2/95, 2%) eyes with a confirmed diagnosis of glaucoma were in the 3-month-old group, and additional surgical interventions were performed in these patients to lower IOP.

As shown in Figure 5, in the patients in the 6-month-old group, the incidence of severe PCO into the visual axis was significantly higher in the surgery A group than in the B and C groups (surgery A: 8, 53.3%; surgery B: 3, 14.3%; and surgery C: 3, 18.8%; *P*=0.03). Throughout the duration of the follow-up period, in the patients who underwent surgery at 3mo, the rate of occurrence of adverse events during the first six months was significantly lower in patients in the surgery B group than in the surgery A and C groups (surgery A: 10, 47.6%;

Table 1 Baseline characteristic of children participating in the study

n (%)

Characteristics	3-month group	6-month group
Gender (patients)	*n*=31	*n*=26
Male	18 (58.1)	15 (57.7)
Female	13 (41.9)	11 (42.3)
Surgical method (eyes)	*n*=62	*n*=52
I/A	21 (33.8)	15 (28.8)
I/A+PCCC	21 (33.8)	21 (40.4)
I/A+PCCC+A-Vit	20 (32.4)	16 (30.8)
Follow-up (person-time)	*n*=324	*n*=281
<6m	120 (37.0)	99 (35.2)
6mo to 2y	108 (33.0)	94 (33.5)
2 to 4y	96 (30.0)	88 (31.3)

None of baseline characteristics were significantly different between the two groups at the 0.05 level. In the initial schedule, 372 appointments were assigned in the 3-month group, and 312 appointments were scheduled in the 6-month group. Of these, 605 (88%) of 684 expected follow-up visits were completed.

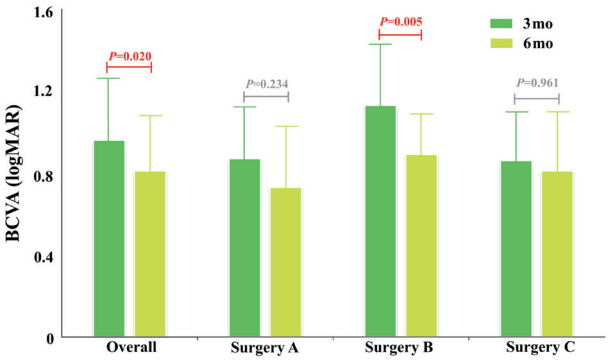

Figure 2 Comparisons of the long-term BCVA between the 3-month-old group and the 6-month-old group in each surgical procedure subgroup The overall logMAR BCVA in the 6-month-old group was better than the 3-month-old group (3-month: 0.96±0.30; 6-month: 0.81±0.28, *P*=0.02), and in each surgical procedure subgroup, the visual outcome in the 6-month group was better (3A *vs* 6A: 0.87±0.26 *vs* 0.73±0.31, *P*=0.234; 3B *vs* 6B: 1.13±0.30 *vs* 0.89±0.20, *P*=0.005; and 3C *vs* 6C: 0.86±0.25 *vs* 0.81±0.32, *P*=0.961). BCVA: Best-corrected visual acuity; Overall: Overall BCVA in the 6-month-old or the 3-month-old group.

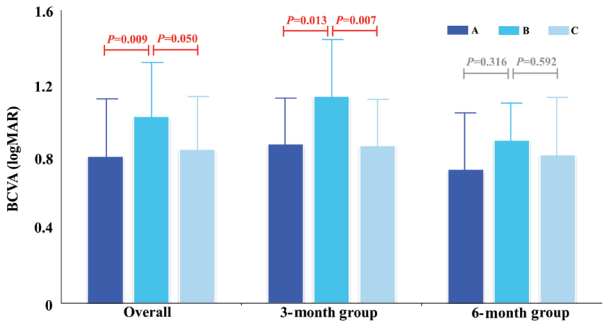

Figure 3 Comparisons of long-term BCVA among the three surgical procedures performed at 3 and 6mo The overall logMAR BCVA in the surgery A group was lower than those in the B and C groups (A: 0.80±0.29, B: 1.02±0.28, and C: 0.84±0.28; *P*=0.007; A *vs* B, *P*=0.009; B *vs* C *P*=0.050). In each surgical timing subgroup, the visual outcome in the B group was the worst (3A: 0.87±0.26, 3B: 1.13±0.30, 3C: 0.86±0.25, *P*=0.003; 3A *vs* 3B, *P*=0.013; 3B *vs* 3C, *P*=0.007; 6A: 0.73±0.31, 6B: 0.89±0.20, 6C: 0.81±0.32, *P*=0.398; 6A *vs* 6B, *P*=0.316; 6B *vs* 6C, *P*=0.592). BCVA: Best-corrected visual acuity; Overall: Overall BCVA in the 6-month-old or the 3-month-old group.

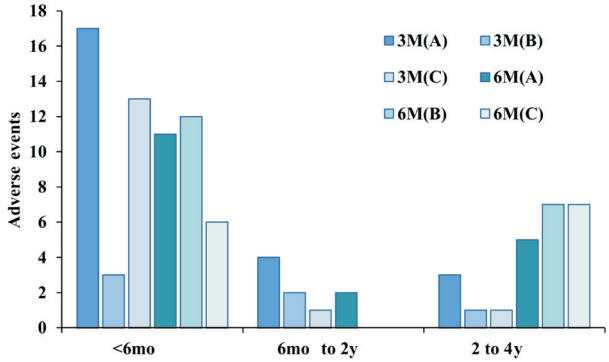

Figure 4 The distribution and proportions of postoperative adverse events at different time points after surgery The majority of adverse events occurred within the first six months (62/95, 65.3%), and very few complications occurred in the mid-term period from 6mo to 2y (9/95, 9.5%). 3M(A): Underwent I/A at 3mo old; 3M(B): Underwent I/A+PCCC at 3-month-old; 3M(C): Underwent I/A+PCCC+A-Vit at 3-month-old; 6M(A): Underwent I/A at 6-month-old; 6M(B): Underwent I/A+PCCC at 6-month-old; 6M(C): Underwent I/A+PCCC+A-Vit at 6-month-old.

surgery B: 3, 14.3%; and surgery C: 11, 55.0%; *P*=0.016). No significant relationship was found between complications and logMAR BCVA through the multivariate linear regression following adjustment for age at which the BCVA value was examined.

Representative Patients Table 2 shows the summary statistics for four representative patients in the 3-month-old group and four patients in the 6-month-old group. All of these patients exhibited good compliance and reliable examination results. In the representative 3-month-old group, patients A, C and D showed poor long-term visual function, whereas patients E, G

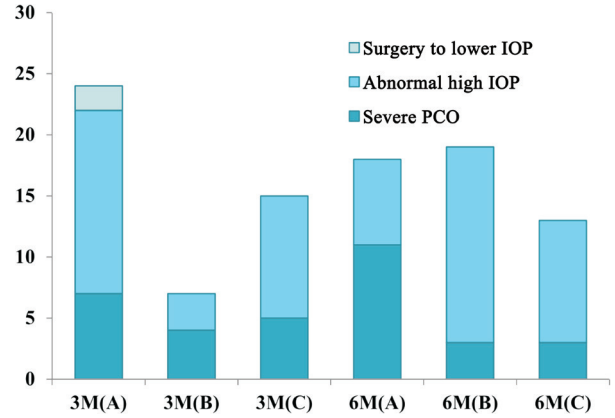

Figure 5 The distribution and proportions of postoperative adverse events in patients who underwent different surgical approaches at different times Lens proliferation into the visual axis (33/95, 34.7%) and abnormally high IOP (60/95, 63.1%) were the most common adverse events. In the patients who underwent surgery at 3-month-old, the rate of occurrence of adverse events in the first six months after surgery B was lower than that in the surgery A and C groups. IOP: Intraocular pressure; PCO: Posterior capsular opacification; 3M(A): Underwent I/A at 3-month-old; 3M(B): Underwent I/A+PCCC at 3-month-old; 3M(C): Underwent I/A+PCCC+A-Vit at 3-month-old; 6M(A): Underwent I/A at 6-month-old; 6M(B): Underwent I/A+PCCC at 6-month-old; 6M(C): Underwent I/A+PCCC+A-Vit at 6-month-old.

and H in the 6-month-old group had better visual outcomes. Patients B, E and H suffered from postoperative complications but had good visual prognosis. Patient D is a typical example of a patient who suffered no complications but had a less than ideal visual outcome.

DISCUSSION

Principal Findings This randomized controlled trial (RCT) investigated postoperative complications and long-term visual outcomes in patients who underwent pediatric cataract surgery at different time points using different surgical methods. We found that the overall logMAR BCVA scores in the 6-month group were better than those in the 3-month group regardless of the surgical procedure subgroup. Moreover, the incidence of severe PCO into the visual axis was significantly higher in the surgery A subgroup than in the B and C subgroups. The multivariate linear regression analysis did not reveal significant differences between the incidence of complications and long-term BCVA. To the best of our knowledge, this is the first two-layer RCT to investigate the effects of both surgical timing and surgical approach on outcomes in congenital cataract surgery.

Implications for Clinicians and Investigators Our results indicate that it might be safer and more beneficial for bilateral total congenital cataract patients to undergo surgery at 6mo than at 3mo. In this study, the overall and subgroup long-term visual outcomes are better in patients who undergo surgery at 6mo of age than those in patients who undergo surgery

Table 2 Representative samples for the 3-month-old group and the 6-month-old group

Patient ID	Laterality	Surgery	Complications (mo)	BCVA (logMAR)	Binocular BCVA	BCVA age (mo)
3-month-old group						
Patient A	OD	B	None	1.4	1.3	48
	OS	C	High IOP (1)	1.4		
Patient B	OD	C	None	0.5	0.31	50
	OS	A	Glaucoma (3); PCO (6)	0.31		
Patient C	OD	A	PCO (36)	0.82	0.68	44
	OS	A	PCO (36)	0.68		
Patient D	OD	B	None	1.3	0.96	46
	OS	B	None	1.1		
6-month-old group						
Patient E	OD	A	PCO (3, 24)	0.5	0.3	47
	OS	A	PCO (3)	0.3		
Patient F	OD	A	High IOP (1/4); PCO (1)	0.68	0.5	50
	OS	B	High IOP (1/4); PCO (1)	0.68		
Patient G	OD	C	None	0.4	0.3	44
	OS	C	None	0.4		
Patient H	OD	A	PCO (1)	0.31	0.31	43
	OS	C	PCO (1)	0.31		

Four representative patients in the 3-month-old group and four in the 6-month-old group are included along with their summary statistics. All of these patients exhibited good compliance and reliable examination results. In the representative 3-month-old group, patients A, C and D had poor long-term visual function, while patients E, G and H in the 6-month-old group had better visual outcomes. Patients B, E and H suffered from postoperative complications but had good visual prognoses. Patient D is a typical example of a patient who suffered no complications but had a less than ideal visual outcome. OD: Right eye; OS: Left eye; A: Underwent I/A surgery; B: Underwent I/A+PCCC surgery; C: Underwent I/A+PCCC+A-Vit surgery; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; PCO: Severe posterior capsular opacification.

at 3mo of age. The best subgroup BCVA scores within the 3-month-old group were not significantly different from the worst subgroup BCVA scores in the 6-month-old group. Both participants with a confirmed diagnosis of glaucoma were in the 3-month-old group, and additional surgical interventions were performed in these patients to lower IOP.

There are a number of implications of these results and several ways in which they could be interpreted. First, the average sleeping time with closed eyes of infants aged from 3 to 6mo is approximately 15h per day, including 5h of daytime sleep, which is similar to the average sleeping time in newborns[34]. These data indicate that light interruption and form-deprivation amblyopia might not be the key factors affecting the development of VA in newborns with congenital cataracts. Second, younger infants have a greater risk of experiencing adverse effects during general anesthesia due to the immaturity of the cardiovascular, pulmonary, thermoregulatory, and gastrointestinal systems, as well as the liver and kidneys, and have a low body weight[35]. It is, in most instances, more difficult and riskier to execute treatment for amblyopia and routine postoperative examinations in uncooperative children who undergo surgery early in life[36]. Third, recent studies have demonstrated that the visual system retains considerable plasticity with significant individual difference, even when early blindness extends beyond the critical periods[37-38]. These results suggest that performing aggressive interventions to achieve early visual experience at the expense of the increased risk associated with anesthesia and postoperative management may be unwarranted, especially for those patients with high plasticity. Further investigation into the heterogeneity in visual outcomes in these patients is greatly needed.

We found that postoperative complications, including secondary glaucoma and visual axis opacity, were treatable in our patients and did not compromise VA outcomes when rigorous follow-up and timely interventions were applied. Our data reveal that I/A tends to induce more PCO, and no significant correlations were found between the rate of occurrence of adverse events and poor VA. Representative patients B, E, F and H suffered postoperative complications but achieved good long-term visual function. These results have potentially important implications. First, I/A+PCCC or I/A+PCCC+A-Vit might inhibit the proliferation of LECs and thereby interrupt the development of PCO. Second, timely interventions, including controlling IOP with medications or surgeries, could substantially reduce the risk and damage caused by postoperative complications[11]. Third, conducting

frequent examinations during the first 6mo after surgery (four times, specifically at 1wk, 1, 3, and 6mo) and using aggressive Nd:YAG laser capsulotomy to ensure the continuous transparency of the visual axis could benefit visual functions.

Interpretation and Comparisons with Other Research Similar to previous studies[11,39], we found that the majority of adverse events occurred within the first six months and that very few complications occurred within the mid-term period from 6mo to 2y following surgery. Moreover, severe PCO and abnormally high IOP were the most common adverse events in each postoperative period. In addition, consistent with previous studies, more severe PCO was observed in the patients who underwent I/A, which confirms the hypothesis that the posterior capsule and the anterior vitreous face act as scaffolds for the proliferation of LECs. Posterior capsulectomy and anterior vitrectomy could therefore interrupt the development of visual axis opacification and accordingly reduce the rate of occurrence of secondary cataracts.

However, several studies have obtained different visual acuity levels in the treated eyes of children who underwent bilateral cataract surgery[7,40-42]. Our BCVA results may have differed from those in other studies for three reasons. First, the participant age at the time of examination in our study was younger (48.72±3.24mo), but the mean age was 5.3y in Lambert's study and 122mo (10.2y) in Young *et al*'s study[40], which would presumably contribute to superior visual outcomes. Second, the method of VA evaluation was different (Teller VA cards for visual resolution in our research *vs* Snellen VA for visual recognition in their studies). The use of Teller VA cards is a well-accepted evaluation method for infants and preverbal children, and although the results are translatable to a Snellen equivalent, this is usually not performed for accuracy reasons. Third, the visual outcomes that we reported are the mean values of all pediatric patients in our study. However, only 60% of children had 20/40 or better VA in the Lambert study, and only 70% were able to complete Snellen VA testing (92% of these results were available) in the Young *et al*'s study[40], which therefore is not likely to represent the actual mean VA levels.

Strengths and Limitations of the Study Our results should be interpreted within the context of the study's strengths and limitations. In this era of precision medicine, we aim to treat patients not only appropriately but also at the right time to prevent unnecessary risks and to improve prognosis[43]. In our investigation, a RCT, which is the most reliable test of a scientific hypothesis[44], was performed. Therefore, the strengths of this study include its two-layer randomized controlled design, which was used to simultaneously investigate the efficiency of surgical timing and methods; the fact that surgeries were performed by two experienced pediatric cataract surgeons using standard operation procedures, ensuring the accuracy of the baseline data in all groups; the fact that a single experienced pediatric optometrist measured visual outcomes using Teller VA cards throughout the follow-up, which minimized bias in infant visual examinations; and our adherence to a unified, strict postoperative regimen and follow-up protocol within the study group (CCPMOH)[24].

The weaknesses of this study include the small sample sizes of the study groups, which limited our statistical power. Moreover, postoperative amblyopia management using spectacles resulted in difficulties in aphakic eyes, which might have resulted in bias and poor efficiency in amblyopia treatments between the groups. Despite these shortcomings, our study is the first RCT to simultaneously investigate the surgical timing of and approach used during lens extraction surgery for bilateral total congenital cataracts in infants.

In conclusion, our findings have several potential implications. Most importantly, our results suggest that performing early interventions for lens removal at 3mo of age may be unwarranted and that primary lens-removal surgery performed at 6mo of age may be a safer and more beneficial choice for postoperative management and visual prognoses in infants with bilateral total cataracts. Interestingly, our results also demonstrate that postoperative complications, including secondary glaucoma and severe PCO, are treatable and do not compromise VA outcomes when combined with rigorous follow-up and timely intervention. Therefore, to achieve better long-term visual outcomes, it might be appropriate to make successful postoperative management the top priority rather than focusing solely on reducing the incidence of adverse events.

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