Advisability of primary intraocular lens implantation for infants under 2: A systematic review and meta-analysis

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Abstract

Purposes: The present meta-analysis compared the postoperative visual performance of primary intraocular lens (IOL) implantation and primary aphakia in cataract infants. Methods: We performed a systematic literature search in PubMed, EMBASE and Science Direct. Postoperative visual acuity (VA) and complications were extracted and pooled. Results: Four randomized controlled trails (RCTs) and seven retrospective studies were included. The postoperative VA in primary IOL group was better than that in primary aphakia group [MD=-0.12, 95% CI: (-0.19, -0.05), p=0.91]. There was no significant difference in the incidence of glaucoma, retinal detachment and nystagmus between primary IOL group and primary aphakia group [OR=1.27, 95% CI: (0.79, 2.05), p=0.84 for glaucoma; OR=0.49, 95%CI: (0.07, 3.30), p=0.34 for retinal detachment;; OR=1.11, 95%CI: (0.62, 1.98), p=0.73 for nystagmus]. Analysis of unilateral subgroup indicated there were fewer infants with strabismus in primary IOL group compared with primary aphakia group [OR=0.40, 95% CI: (0.21, 0.79), p=0.46]. The primary IOL group needed more visual axis opacification (VAO) clearing than primary aphakia group [OR=9.33, 95%CI: (5.21, 16.73), p=0.27]. Conclusion: Primary IOL implantation provided more visual benefits. IOL implantation may decrease the incidence of strabismus in comparison with primary aphakia in unilateral subgroup. However, these advantages could be offset by a higher VAO clearing surgery.

Extra information

How did you gather the information you considered in your review?

We performed a systematic search in PubMed, Science Direct, EMBASE and Cochran Library. One or a combination terms was used in the search. The publication time of the literature was restricted from January 1, 2000 to August 2, 2020. Two investigators searched and screened the articles independently. In case of disagreement about the literature search, a third reviewer would engage in the discussion until a consensus was reached.

What is the 'take-home' message for the clinician?

We found the postoperative VA of primary IOL group was better than that of primary aphakia group. Actually, constant optical correction during this crucial period is very important for children. Moreover, previous studies indicated primary IOL implantation was a protective factor of secondary glaucoma. Whereas we found there was no difference in the incidence of glaucoma surgery between this two groups. These two critical findings help the surgeons to weigh the visual benefits and the risks of surgery when they choose IOL implantation for a children younger than 2 years.

Keywords : Primary intraocular lenses, Primary aphakia, Cataract surgery, Cataract infant;

Introduction

Approximate 1.4 million children suffer from blindness around the world.[1] Childhood preventable blindness has been identified as a priority of the Vision 2020: "The Right to Sight"[2]. Pediatric cataract is the leading cause of treatable childhood blindness and accounts for 5 - 20% of childhood blindness[3-5]. IOL implantation is the main option for optical rehabilitation in children after cataract surgery. There are two main surgical procedures for IOL implantation in cataract infants, i.e. primary IOL implantation and primary aphakia followed by secondary IOL implantation. Due to the risk of postoperative complications, such as inflammatory responses, VAO and secondary glaucoma, IOL implantation in cataract children older than 2 years has been a consensus among pediatric cataract surgeons around the world[6-9]. But in other cases, children with aphakic spectacles or contact lenses are susceptible to VA issues, corneal problems, compliance with lens-wearing and high cost.

Many studies had reported the clinical performance (including VA and postoperative complications) after congenital cataract surgery[7,10-12]. However, given the elongation of axial length, change of corneal curvature and high incidence of additional surgery, the benefits and risks of primary IOL implantation in cataract infants, especially in those younger than 2 years, still remains a controversial issue[13-15]. Surgeons need to weigh the visual benefits agains risk (such as inflammatory response, VAO and secondary glaucoma associated with the procedure) of surgery when they choose IOL implantation for a children younger than 2 years.

Glaucoma is the main complication of congenital cataract surgery and has been discussed in many studies[16-18]. However, there is no consistent conclusion on which type of surgery can decrease the incidence of glaucoma. Some studies suggested that primary IOL implantation was a protective factor of glaucoma after cataract surgery[19,20]. Whereas, other studies suggested that the incidences of glaucoma were comparable in primary IOL group and primary aphakia group [11,21,22]. Similarly, previous studies didn't reach consensus on which type of procedure would be better in terms of postoperative VA and complications[23,24]. Therefore, the present meta-analysis aims to compare the postoperative performance of primary IOL implantation and primary aphakia in cataract infants younger than 2 years, and provide solid evidence for better clinical practice.

Materials and methods

Search strategy

A systematic search was performed in PubMed, Science Direct, EMBASE and Cochran Library. One or a combination of the following terms was used in the search: congenital, infant, child, pediatric, cataract, intraocular lens, IOL, primary, secondary, pseudophakia, aphakia, cataract surgery, comparison and compare. The publication time was restricted from January 1, 2000 to August 2, 2020. Two investigators (Shanshan Jin and Jingshang Zhang) searched and screened the articles independently. In case of disagreement about the literature search, a third reviewer (Xiuhua Wan) would engage in the discussion until a consensus was reached. Figure 1 showed the selection process.

Inclusion and exclusion criteria

Inclusion and exclusion criteria: (i) The subjects should be cataract infants younger than 2 years (P) who received cataract extraction with primary IOL implantation (I) or primary aphakia (C); (ii) The clinical outcomes on postoperative VA, complications (glaucoma, strabismus, nystagmus and visual axial opacity) (O) should be evaluated; (iii) Given the age at the surgery and the age at the last visit were significant factors for the postoperative outcomes in congenital cataract patients, studies in which the age at the surgery or last visit in these two groups did not match were excluded; (iv) Studies without detailed outcome on the postoperative visual performance were excluded; (v) Studies reporting data on individual patient rather than individual surgery eye were excluded; (vi) (potentially) overlapping study populations that reported same outcome were excluded; (vii) Non-English publications were excluded.

Data extraction

Data were extracted using pre-defined data fields from each study by two investigators independently. If there were inconsistencies between two investigators, a third reviewer would extract results and engage in discussion until a consensus was reached. VA reported as log MAR VA were extracted as the primary outcome. Second outcomes including glaucoma, strabismus, nystagmus and VAO were extracted. The results of postoperative visual performance at last visit were extracted from studies with multiple postoperative follow-up data. As for the retrospective studies, age-matched outcome would be extracted if reported. Continuous data reported as mean ± SD were extracted directly. Those data reported as median and interquartile ranges would be converted into mean and SD based on the formula[25].

Quality assessment

The quality of the included RCTs was assessed with the Cochrane Risk of Bias Tool[26]. It contained six domains: randomization process, intervention deviation, missing outcome data, outcome measurement, selective outcome reporting. The retrospective studies were assessed by the Newcastle-Ottawa Scale (NOS) in the following 3 aspects: cohort selection, cohort comparability, assessment of outcome[27]. Details of NOS were available in Appendix 1.

Data synthesis and statistical analysis

The statistical analysis was performed with the statistical software open source R program (Version 3.41). Categorical outcomes were estimated by odds ratio (OR) with 95% CI. If "1" falls into the CI, the outcome would be considered "not statistically significant". The mean difference (MD = mean of primary IOL – mean of primary aphakia) with a 95% confidence interval (CI) was adopted for continuous outcomes. If "0" falls into the CI, the outcome would be considered "not statistically significant".

Heterogeneity across studies was tested with Q test and I^2 statistic. If there was no heterogeneity across these studies (I^2¡50%), the Mantel–Haenszel fixed-effect model would be used. I^2 above 50% and the P-value below 0.1 would constitute a significant heterogeneity among these studies, and possible reasons would be explored by reviewing the included studies. Three approaches were used to detect the source of heterogeneity in this meta-analysis: sensitive analysis, subgroup analysis and meta regression. Through sensitivity analysis, we could determine whether the heterogeneity would decrease following exclusion of each study one by one. Subgroup analysis and meta regression would be performed according to the clinical characteristics of the included studies. Through these two approaches, we could identify the factor that induced heterogeneity in the meta-analysis. If sensitivity analysis and subgroup analysis did not decrease the heterogeneity, the random-effects model (DerSimonian-Laird) would be adopted to calculate pooled effect size.[28,29].

Results

Characteristics of included studies

Four randomized controlled trails (RCTs) and seven retrospective studies were included. Table 1 describes the characteristics of the 11 included studies that were published during 2001-2018. The surgery age of subjects ranged from 1.8-7.5 mouth. The follow-up duration ranged from 0.5-5 years.

Risk of bias assessment

Three RCT studies reported the randomization process, intervention deviation, yet none of them had selective reporting and outcome data missing. The study of Qian L[30] did not describe the approach of random sequence generation and potential intervention deviation. Vasavada et al.[22] reported that the surgery type was revealed to the surgeon and outcome examiner in their study. The details of risk assessment for these RCTs were presented in the Figure 2.

Retrospective studies were assessed based on NOS. Five studies described the detailed process of cohort selection, and were assessed to be of low risk in cohort selection. The study by Autrata et al.[31] did not report the source of study subjects, and was assessed to be of medium risk in cohort selection. High risk was found in the cohort selection in the study by Trivedi et al[32], as the source and preoperative data on patients were not described. Given the age at the surgery and the age at the last visit were significant factors for the

postoperative outcomes in cataract infants, these two factors were used to assess the cohort comparability. According to our inclusion and exclusion criteria, all these retrospective studies have similar age at surgery and last visit in both groups. So, all these studies were assessed to be of low risk in the cohort comparability. The study by Trivedi et al[32]. was assessed to be of high risk since they did not report the duration of follow up and rate of follow-up loss. Except for the above study, all the other studies gave detailed information on outcome assessment. The details of risk assessment for these retrospective studies were shown in the Figure 3.

Visual acuity

There were 7 studies reporting VA[11,22,30,31,33-35], and the VA of primary IOL group was similar to that of primary aphakia group [MD=-0.12, 95%CI: (-0.19, -0.05), p=0.91]. There was no heterogeneity (I^2 =0%)(Figure 4). No publication bias was found (Table 2).

Glaucoma

Glaucoma was reported in 7 studies[11,22,30,32,34,36,37], there was no heterogeneity (I^2=0%). Therefore, the fixed effect model was applied. As shown in Figure 5, there was no difference in the incidence of glaucoma between primary IOL group and primary aphakia group [OR=1.27,95%CI: (0.79, 2.05), p=0.84].

Strabismus

As Figure 6 shows, 6 studies reported the data on strabismus[11,22,31,33-35]. There were much fewer infants with strabismus in primary IOL group compared with primary aphakia group after the surgery [OR=0.53, 95% CI: (0.31, 0.90), p=0.19]. Given the unilateral cases or bilateral cases will be a critical factor that contribute to strabismus incidence after congenital cataract surgery, a subgroup analysis was performed. There were much fewer infants with strabismus in primary IOL group compared with primary aphakia group in the unilateral subgroup [OR=0.40, 95% CI: (0.21, 0.79), p=0.46]. No difference was found in the bilateral subgroup.

Nystagmus

Four studies reported the outcome on nystagmus incidence[22,34,35,38], and no heterogeneity was found (I^2 = 0%). No statistically difference was found between the primary IOL and primary aphakia group in terms of nystagmus [OR=1.11,95%CI: (0.62, 1.98), p=0.73] (Figure 7).

Retinal detachment

As shown in Figure 8, only 2 studies reported data on RD[11,34], and there was no statistical heterogeneity among these studies (I^2 = 0%). No statistically significant difference was found between the two groups [OR=0.49, 95%CI: (0.07, 3.30), p=0.34].

Visual axial opacity clearing

VAO clearing was reported in 5 studies[11,22,34,37], and the I^2 was 23%. As shown in Figure 9, the primary IOL had a significantly higher incidence of VAO clearing compared with primary aphakia, [OR=9.33, 95%CI: (5.21, 16.73), p=0.27].

Discussion

The present meta-analysis demonstrated that the postoperative VA in primary IOL group was better than that in primary aphakia group. These results were consistent with previous studies. Birch et al showed that IOL may support better VA development when a cataract was extracted after age 1, while the difference would taper off with the age reaching 4 years[39,40]. Vasavada et al[22]. reported that more infants in primary IOL group had documentable VA than aphakia group during early postoperative follow-up, and this trend continued until age 5. This result indicated that the visual rehabilitation was faster in pseudophakia group, especially in early postoperative follow-up. However, in the IATS study, the VA was similar in IOL group and contact lens group both in the first (1 year old)[6] and last follow-up (4.5 years old)[11]. This could be explained by better compliance of contact lenses or spectacles in the aphakia group. The IATS study offered

free contact lenses and spectacles for the enrolled subjects. Moreover, trained personnel assessed the vision and monitored the compliance through regular home visits. [41] This may not be carried out in the real world, particularly in developing countries. Actually, constant optical correction during this crucial period is very important for children. A faster visual rehabilitation will impact the activity and overall functional development of the children. Therefore, primary IOL implantation may provide better VA for pediatric patients, especially those under age 5.

Our meta-analysis did not see any difference in glaucoma incidence. Many hypotheses proposed the mechanisms of glaucoma after infantile cataract surgery. However, there is no unanimous conclusion. The mechanisms of secondary glaucoma of pseudophakia eyes and aphakic eyes might be different. The filtration angle of infants is susceptible to postoperative inflammation. Thus, IOL implantation in infants will cause chronic inflammations that induce changes of iris root or trabecular meshwork (TM)[42-44]. This might explain the glaucoma in pseudophakia eyes. As for aphakic glaucoma, since the mechanical absence of lens in the eye, TM cells would be exposed to the lens epithelial cells (LEC). Michael et al. specified that LEC induced changes in TM cells that resembled changes in primary open-angle glaucoma[45,46]. It is worth noting that the mechanism of glaucoma is still unclear. But we could not make any attempt to investigate the mechanisms of secondary glaucoma after infantile cataract surgery in this meta-analysis.

Analysis of unilateral subgroup indicated there were much fewer infants with strabismus in primary IOL group compared with primary aphakia group. This was consistent with the studies by Autrata et al[31]. and Lambert et al. Previous studies also suggested that the incidence of strabismus in IOL group was relatively low[47-49]. The absence of natural lens in unilateral eye will lead to anisometropia and aniseikonia, which are related to secondary strabismus following congenital cataract surgery. Primary IOL implantation offers a stable retinal image with minimal aniseikonia as well as full-time optical correction for surgery eye. Moreover, children have to wear contact lenses or spectacles to get optical correction in case of absent lenses. The compliance of wearing contact lenses will be affected by the complications associated with contact lenses like corneal infection. Hence, this might explain the higher incidence of strabismus in primary aphakia group.

Postoperative VAO is very common in infants after congenital cataract surgery. According to the previously published literatures, IOL implantation is associated with higher VAO incidence in congenital cataract children, especially those younger than 6 months[50-52]. The average incidence of VAO after IOL implantation is 44.0%, while the incidence is up to 80% when the patient is younger than 6 mouths[53]. The IOL in capsular bag acts as an obstacle and prevents the anterior and posterior capsule leaflets from fusing, while the capsule edges will seal more effectively in aphakic eye. In our meta-analysis, primary IOL group had a noticeably higher incidence of VAO clearing than primary aphakic group, which was consistent with the RCT study conducted by IATS and other previous studies.[11,34,54,55].

Our meta-analysis has some limitations. First, even though this meta-analysis is the first systematic review on this topic, it included retrospective studies rather than just RCTs. Thus, the level of evidence will be weakened by the inclusion of retrospective studies. However, there is no denying that it is very difficult to conduct RCT among paediatric cataract children. Second, the pooled effect of complication, especially the glaucoma incidence, might be affected by the inconsistent diagnostic criteria adopted in these studies. Third, the control group of these included studies was either primary aphakia followed by contact lens or primary aphakia followed secondary IOL implantation. Third, given the number of patients in each study is relatively small, we could not draw explicit conclusion on the difference in postoperative visual performance.

Conclusions

In summary, the postoperative VA in primary IOL group was better than that in primary aphakia group. Primary IOL implantation may be of lower incidence of strabismus than those with primary aphakia. However, these advantages could be offset by higher surgery incidence especially VAO clearing.

Contributorship statement

We thank for support by the sources of funding in this study. Study design and concept of this meta-

analysis were carried out by Xiu Hua Wan, Jingshang Zhang, Jinda Wang and Shanshan Jin; Shanshan Jin and Jingshang Zhang conducted the data collection; Shanshan Jin and Kai Cao performed the data analysis; Ying Xiong, Guyu Zhu, Jing Li and Hailong He provided interpretation of the data. Shanshan Jin performed the first draft of the manuscript; Shanshan Jin, Jingshang Zhang, Jinda Wang and Xiu Hua Wan revised the manuscript and produced the final version; English polishing was done by Mayinuer Yusufu.

Competing interests

There is no conflict of interest

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Table 1. Characteristics of the included studies (n = 10).

Study	Year	Designs	Primary IOL	Primary IOL	Primary IOL	Primary aphakia
			N(eye)	Age at Surgery (months)	Age at last visit (years)	N(eye)
IATS group	2014	RCT	57	1.8	4.5	57
Vasavada A R	2018	RCT	29	6.3	¿5	25
Felius J	2014	RCT	57	1.8	4.5	57
Lambert SR	2001	RS	12	2.8	1.5	13
Trivedi R H	2006	RS	41	1.9	¡1	42
Magli A	2013	RS	30	7.2	9.5	36
Lambert SR	2004	RS	12	2.8	4.3	13
Autrata R	2005	RS	18	3.4	4.9	23
Joshaghani M	2015	RS	23	7.5	7.0	32
Wong B	2009	RS	37	4.3	¡3	61
Qian L	2014	RCT	30	¡24	¡3	30

Indicators	t	df	p
VA	1.904	5	0.115
Glaucoma	1.075	5	0.331
Strabismus	-0.345	4	0.748
Nystagmus	-0.832	2	0.493
Retinal detachment	-0.438	1	0.737
Glaucoma surgery	87.023	1	0.007
Strabismus surgery	-0.879	2	0.472
VAO clearing	-2.586	3	0.081

Table 2. Egger's test for each outcomes

Figure legend

Figure 1. Flow chart of study selection

Figure 2. Risk of bias graph of RCT studies.

Figure 3. Risk of bias graph of retrospective studies.

Figure 4. Forest plot of VA.

Figure 5. Forest plot of glaucoma.

Figure 6. Forest plot of strabismus after subgroup analysis.

Figure 7. Forest plot of nystagmus.

Figure 8. Forest plot of retinal detachment.

Figure 9. Forest plot of VAO clearing.

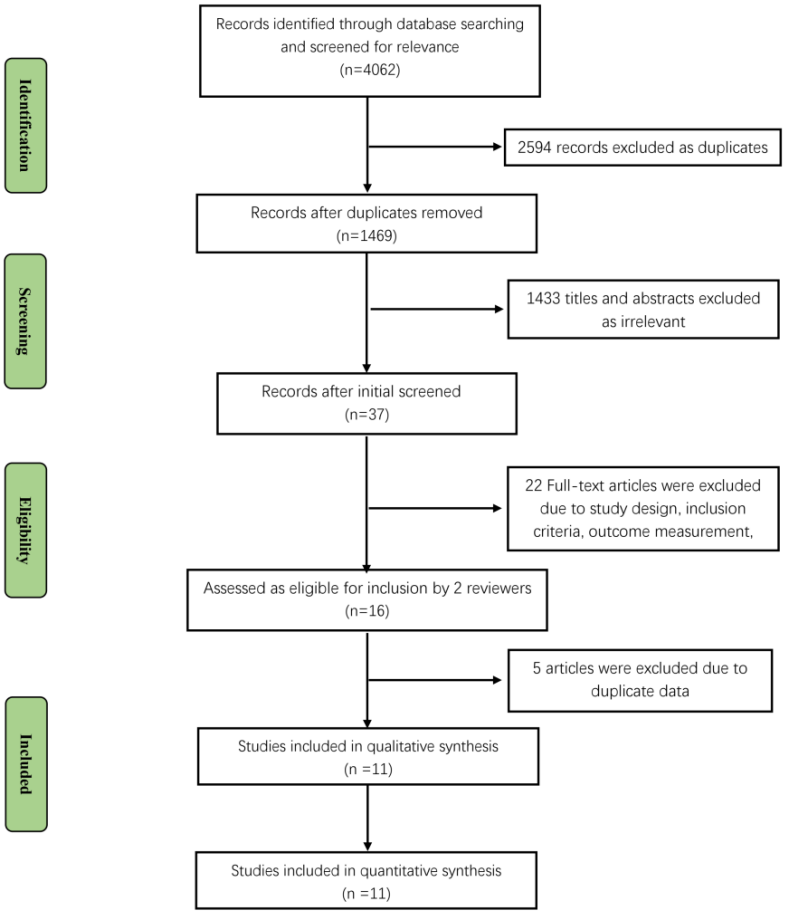

Figure 1. Flow chart of study selection

Study	IOL Total	Mean	SD	Aphakia Total	Mean	SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
IATS group 2014	57	0.90	0.9900	57	0.90	0.9600		0.00	[-0.36; 0.36]	3.6%	3.6%
Vasavada A R 2018	29	0.50	0.2300	25	0.59	0.3300		-0.09	[-0.24; 0.06]	19.5%	19.5%
Lambert SR 2001	12	0.70	0.3200	13	0.87	0.3100		-0.17	[-0.42; 0.08]	7.5%	7.5%
Magli A 2013	15	0.53	0.3600	18	0.54	0.4000		-0.01	[-0.27; 0.25]	6.9%	6.9%
Autrata R 2005	18	0.43	0.3300	23	0.58	0.3900		-0.15	[-0.37; 0.07]	9.5%	9.5%
Joshaghani M 2015	23	0.85	0.7300	32	0.89	0.5600		-0.04	[-0.40; 0.32]	3.6%	3.6%
Qian L 2014	30	0.50	0.1700	30	0.65	0.2100		-0.15	[-0.25; -0.05]	49.4%	49.4%
Fixed effect model	**184**			**198**				**-0.12**	**[-0.19; -0.05]**	**100.0%**	**--**
Random effects model								**-0.12**	**[-0.19; -0.05]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$