Review Article

Efficacy and safety of vitrectomy for congenital cataract surgery: a systematic review and meta-analysis based on randomized and controlled trials

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ABSTRACT.
Purpose: To explore the effectiveness and safety of vitrectomy for congenital cataract surgery.
Methods: We searched PubMed, Science Direct, The Cochrane Library, China National Knowledge Infrastructure and the Wanfang Database. Two researchers extracted data and assessed paper quality independently. Posterior capsule opacification (PCO) or visual axis opacification (VAO), reoperation rate, visual acuity, intraocular lenses (IOL) deposit, synechias, uveitis, secondary glaucoma, low-contrast sensitivity and IOL decentration were compared.
Results: We included 11 randomized controlled trials (RCTs) with 634 congenital cataract eyes. Cases of posterior capsule opacification in vitrectomy group were significantly less than that of control group, with risk ratio (RR) of 0.15 [95% confidence interval (CI): 0.09, 0.26], and there was no heterogeneity ($I^2 = 0\%$, $p = 0.94$). Reoperation rate in vitrectomy group was lower than that of control group (RR = 0.40, 95%CI: 0.17, 0.94), and there was no heterogeneity ($I^2 = 0\%$, $p = 0.85$). Best-corrected visual acuity (BCVA) measured in LogMAR unit of vitrectomy group was smaller, with a mean difference (MD) of $-0.17$ (95%CI: $-0.28$, $-0.05$), and $I^2$ was only 22%, indicating of a small heterogeneity. No statistical difference was found between two groups on IOL deposit (RR = 1.23, 95%CI: 0.70, 2.17), and the heterogeneity was small ($I^2 = 16\%$, $p = 0.31$). No statistical difference was found between two groups on synechias (RR = 1.08, 95%CI: 0.60, 1.94), with a quite small heterogeneity ($I^2 = 3\%$, $p = 0.38$). No statistical difference was found between two groups on uveitis (RR = 0.55, 95%CI: 0.15, 2.01), and there was no heterogeneity ($I^2 = 0\%$, $p = 0.94$). There was no statistical difference on IOP either, with a MD of 0.25 (95%CI: $-1.56$, 2.07), and there was no heterogeneity ($I^2 = 0\%$). Egger’s test showed that there was no publication bias for all assessed outcomes. Low-contrast sensitivity was better in the vitrectomy group. And no evidence indicated vitrectomy could lead to a higher risk on secondary glaucoma or IOL decentration.
Conclusion: Vitrectomy helps lower the PCO risk and reoperation risk after congenital cataract surgery, and also, vitrectomy helps patients gain a better BCVA and achieve a better low-contrast sensitivity, with no trade-off on IOP control, IOL deposit, synechias, uveitis and secondary glaucoma. We recommend performing vitrectomy during congenital cataract surgery.

Key words: congenital cataract – intraocular lenses implantation – opacification – paediatric – vitrectomy

Introduction
In congenital cataract patients, visual axis opacification (VAO) makes up more than 40% of all complications after surgery (Shrestha & Shrestha 2014); hence, many surgery types had been proposed to help patients keep a clear visual axis, such as primary posterior capsulotomy, pars plana lensectomy and primary posterior continuous curvilinear capsulorhexis (PCCC) (Gimbel & DeBroff 1994; Vasavada et al. 2011; Sigler & Calzada 2014).
Some researchers suggested anterior vitrectomy as a routine for primary capsulotomy (Tablante et al. 1988; Mackool 1994). Meanwhile, some other researchers, like Vasavada A (Vasavada & Desai 1997), suggested that anterior vitrectomy should be done along with primary PCCC for congenital cataract children younger than 5 years old because age was a very important issue. In Japan, a survey (Nagamoto et al. 2015) on surgical treatment for congenital cataract was carried out in 34 medical facilities. Results showed that doctors preferred a small incision surgery with implantation of an acrylic foldable IOL into the capsular bag combined with posterior capsulotomy, while vitrectomy would be only performed in patients under 6 years old. A similar observation was reported by Petric I (Petric & Lacmanovic 2004) who suggested a joint operation of anterior vitrectomy and posterior capsulorhexis during cataract surgery for young children. Evidence from some interventional studies also favoured vitrectomy, during 2011 to 2013, Ma (2013) randomly assigned 106 congenital cataract children aged 2–9 years old to accept vitrectomy or not when performing PCCC. After a 3-year follow-up, 27 eyes in PCCC group had VAO while in PCCC plus vitrectomy group only 4 eyes had VAO. Another interesting thing was that from Ma X’s study, age was not a reason for deciding whether vitrectomy should be performed or not.

However, there was also some evidence against vitrectomy. Back to 1990s, Gimbel HV (Gimbel & DeBroff 1994) described the effectiveness of posterior capsulorhexis with optic capture, where vitrectomy was not performed, on maintaining a clear visual axis after paediatric cataract surgery. Later, in 1997, Fenton S (Fenton & O’Keefe 1999) followed 22 eyes undergoing primary posterior capsulorhexis without vitrectomy for 19 months, and it turned out that 27 eyes kept a clear visual axis. Kim KH (Kim et al. 2008) retrospectively assessed 92 congenital cataract eyes of 61 children aged younger than 1 year old and found that anterior vitrectomy did not reduce post-operative complications, and the VAO rate was still high either. Even the interventional studies gave negative answer, Mullner-Eidenbock A (Mullner-Eidenbock et al. 2003) performed vitrectomy randomly for 50 eyes of 34 children aged 2–5.9 years old during foldable acrylic AcrySof intracocular lens implantation. After 20.73 months of follow-up, no difference for VAO rate was found between the patients who received vitrectomy and those who did not. A similar result was reported in a group of children aged 10–15 years old by Jafarinasab MR (Jafarinasab et al. 2008) and in another group of children aged 3–12 years old by Raina UK (Raina et al. 2004) in another two RCTs.

Whether vitrectomy is necessary for congenital cataract surgery remains unclear. Our study aims to provide a high-quality evidence based on RCTs.

Materials and Methods

Inclusion criteria

Any included study must be a RCT, the target population should be congenital cataract children receiving IOL implantation, either with vitrectomy or not.

Databases and search strategy

PubMed, Science Direct, the Cochrane Library, the Chinese National Knowledge Infrastructure and the Wanfang Database were searched with one or a combination of the following terms: congenital, infant, pediatric, children, cataract, vitreous, and vitrectomy. Details of the search strategy are available in Appendix #. The publication date was from the beginning to November 31, 2017.

Outcomes and outcome measurement

1. VAO or Posterior capsule opacification (PCO), which is defined as lens epithelial cells proliferation extending into the pupillary space and covering the visual axis. Three studies used slitlamp to diagnose VAO: one study used an Evaluation of Posterior Capsule Opacification (EPCO) computer analysis system developed by Tetz et al. (Tetz et al. 1997); one study diagnosed VAO by retroillumination if there were bubble-like clear spaces within the opacification; one study graded VAO according to the extent of involvement of the posterior capsule.

2. Secondary surgery, referring to reoperation due to occurrence of after cataract.

3. Best-corrected visual acuity, one study used a complete set of Teller visual acuity (VA) cards (Stereo Optical Company, Inc., IL, USA) to measure the monocular and binocular best-corrected visual acuity (BCVA); one study did not report the measurement tool.

4. Deposit, cells and pigments on the IOL optic, which were mostly recorded using a slitlamp microscope.

5. Synchias, which was mostly recorded using a slitlamp microscope.

6. Uveitis, one study used slit lamp to make measurement; one study did not report the measurement tool.

7. Intraocular pressure (IOP), one study measured IOP with a Schiotz tonometer; one study did not describe the measurement tool.

8. Contrast sensitivity, the measurement condition was not stated.

9. Secondary glaucoma.

10. IOL decentration.

Data extraction

We extracted data of all outcomes measured at the last follow-up time. Specifically, for categorical data, all patients who accepted the assigned treatment and attended the last-time follow-up were included; the number of the following events was extracted: PCO, reoperation, deposit, synchias and uveitis; for continuous data, such as BCVA, we extracted the mean value and standard deviation (SD). For BCVA data, only those recorded using logMAR unit were extracted.

Assessment on risk of bias and paper quality

We used the risk of bias tool recommended by the Cochrane Collaboration (http://training.cochrane.org/handbook) to access risk of bias from the following 6 aspects: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting. Specifically, if there were contents describing how the random sequence was generated or allocated, how the blind method was applied, how the outcomes were measured and how the missing data was dealt, the risk of bias would be assessed as ‘low’
level. For example, if the random sequence was generated by random number table or pseudo-random numbers using statistical software, the risk of bias would be assessed as ‘low’ level.

On the contrary, if there were evidence showing random sequence was generated by an inappropriate way, or there was no allocation concealment measure, a ‘high’ level would be labelled for risk of bias. If there were evidence indicating that researchers or those who assess the outcomes know about what treatment was done to the subjects, a ‘high’ level would be labelled for risk of bias. If there were evidence indicating that not all outcomes or missing data were reported, a ‘high’ level would be labelled for risk of bias either. For example, if a random sequence was generated using subjects’ date of hospital admission, the risk of bias for the generation of random sequence would be considered high. By comparing the published RCT study and its protocol, it may be found that one or more preset indicators were not reported, in that case, the risk of bias for selective reporting would also be considered high.

If no information could be obtained, or it was hard to make judgement, an ‘unclear’ label would be marked.

Data synthesis and statistical analysis
We used MD and RR (MD = mean value of vitrectomy group minus mean value of control group) with their 95% CI to estimate continuous outcomes and categorical outcomes, respectively. We finished all the analyses using open source R program (version 3.4.4). Before estimating the pooled effect, we firstly assessed the heterogeneity across studies using $Q$ test and $I^2$ statistic. $I^2$ describes the percentage of variability in effect estimates that is due to heterogeneity rather than to chance. In this study, $I^2$ was all below 25%, and thus, there was only a small heterogeneity and we applied a fixed-effects model to calculate pooled effect size (Borenstein et al. 2010). We furtherly used Egger’s test to test publication bias (Egger et al. 1997). We set the significance level to be 0.05, two-tailed.

Results
After paper selection (Fig. 1), we included 11 RCTs (Vasavada et al. 2001, 2004, 2017; Zhu et al. 2002; Mullner-Eidenbock et al. 2003; Raina et al. 2004; Kugelberg et al. 2005; Rastogi et al. 2007; Jafarinasab et al. 2008; Ma 2013; Lin et al. 2017) with 634 congenital cataract eyes in the analysis.

Fig. 1. Flow chart of paper selection.

Table 1. Characteristics of included RCT studies.

| ID | Author | Year | Age | Sample size | Follow-up (month) |
|----|--------|------|-----|-------------|-------------------|
| 1  | Vasavada | 2001 | 5–12 years | 21 20 | 21.04 |
| 2  | Zhu     | 2002 | 2–6 years  | 38 42 | 24   |
| 3  | Mullner-Eidenbock | 2003 | 2–5.9 years | 20 30 | 20.73 |
| 4  | Raina   | 2004 | 3–12 years | 4  6  | 6–14 |
| 5  | Vasavada | 2004 | 0.2–16 years | 15 14 | 27.60 |
| 6  | Kugelberg | 2005 | 3–15 years | 38 28 | 24   |
| 7  | Rastogi | 2007 | 2–12 years | 10 10 | 14.20 |
| 8  | Jafarinasab | 2008 | 10–15 years | 8  9  | 18.70 |
| 9  | Ma      | 2013 | 2–9 years  | 92 90 | 7–36 |
| 10 | Lin     | 2017 | 3–6 months | 42 36 | 48.70 |
| 11 | Vasavada | 2017 | 0–4 years  | 30 31 | 12   |

Note: In Lin HT’s research, subjects were separated into two groups: 3-month-old group and 6-month-old group, and data were reported separately.
Subjects’ age ranged from 0.2 to 16 years old. The follow-up time ranged from 7 to 48.7 months (Table 1).

The risk of bias of all the included studies was shown in Fig. 2 and Fig. 3. Most studies were assessed as low risk on random sequence generation and selective reporting except for Ma X’s study, because Ma X only reported results on VAO and visual acuity, while no any other information could be found. In addition, the study protocol of Ma X’s research was not available, and there was a ‘high’ risk of selective reporting. Most studies did not state clearly on the random sequence allocation, masking and data processing; therefore, risk on these three aspects was not clear.

We found less VAO cases in vitrectomy group than of control group, with a RR of 0.15 (95% CI: 0.09, 0.26). There was no heterogeneity among studies, with an $I^2$ of 0% and a p value of 0.94 (Fig. 4). Therefore, a fixed-effect model was applied. Egger’s test showed that there was no publication bias, $p = 0.66$ (Table 1).

$I^2$ by heterogeneity test of reoperation rate, visual acuity, deposit, synechias and uveitis were 0%, 20%, 16%, 3% and 0%, respectively, and all $I^2$ was quite small. Fixed-effect model showed that reoperation rate of vitrectomy group was lower than of control group, and the RR was 0.40 (95% CI: 0.17, 0.94) (Fig. 5 and 6). BCVA measured in logMAR unit of vitrectomy group was smaller than of control group, with a MD of $-0.17$ (95% CI: $-0.28$, $-0.05$). No statistical difference was found on deposit, synechias and uveitis, and the RRs were $1.23$ (95% CI: 0.70, 2.17), $1.08$ (95% CI: 0.60, 1.94) and $0.55$ (95% CI: 0.15, 2.01), respectively (Figs 7–9). There was no publication bias for all assessed outcomes by Egger’s test (Table 2).

Only one study recorded the results on low-contrast sensitivity, secondary glaucoma and IOL concentration. The low-contrast sensitivity was $144.89 \div 96.74$ (Table 3) in vitrectomy group and $72.33 \div 46.23$ in control group after surgery, and the difference was obvious. In vitrectomy group, two cases of secondary glaucoma and one case of IOL decentration occurred, while neither occurred in the control group (Table 4). However, no pooled estimation could be obtained due to the limited number of studies.

There was no statistical difference for IOP, with a MD of $0.25$ (95% CI: $-1.56$, 2.07), and $I^2$ was 0% (Fig. 10).

**Discussion**

High risk of VAO had always been a challenge for congenital cataract surgery management, and vitrectomy was proposed as an effective way to reduce the VAO risk for a long time. Nevertheless, conclusions from different studies contradicted with each other,
even some interventional studies gave completely contradictory answers. Hence, we conducted a system review and meta-analysis to summarize a stronger evidence based on published RCTs.

From this review, evidence is clear that vitrectomy helps reduce the VAO risk after cataract surgery. Although 4
out of 7 included studies reported a VAO rate of no statistical significance, all the point estimates were on the left side of the invalid line, and no study reported more VAO cases in vitrectomy group.

Table 2. Results of Egger’s test.

| Variables   | t    | df  | p      |
|-------------|------|-----|--------|
| VAO         | -0.47| 5   | 0.66   |
| Reoperation | 0.22 | 1   | 0.71   |
| Deposit     | 1.62 | 3   | 0.20   |
| Synechias   | 0.62 | 2   | 0.60   |
| VA          | -0.57| 1   | 0.70   |
| Uveitis     | -    | -   | -      |
| IOP         | -    | -   | -      |

Table 3. Extracted result on low-contrast sensitivity.

| Study (year)   | Vitrectomy group | Control group |
|----------------|------------------|---------------|
|                | Sample size | Mean  | SD  | Sample size | Mean  | SD  |
| Vassavada 2001| 21         | 144.89| 96.74| 20         | 72.33 |46.23|

Table 4. Extracted result on secondary glaucoma and IOL decentration.

| Study (year)      | Indicators | Vitrectomy group | Control group |
|-------------------|------------|------------------|---------------|
|                   | Sample size | Cases | Sample size | Cases |
| Vassavada et al. (2017) | Secondary Glaucoma | 30 | 2 | 26 | 0 |
| Mullner-Eidenbock et al. (2003) | IOL decentration | 38 | 1 | 42 | 0 |

Theoretically, VAO could cause a decline of visual acuity and a secondary surgery. Vitrectomy helps prevent VAO and thus helps patients achieve a better visual acuity and reduce the reoperation risk, which is in accord with what we found in this meta-analysis.

Elevated IOP had been reported by some researchers (Yuan et al. 2017) as a common complication after vitrectomy. IOP of vitrectomy group by this review was indeed slightly higher than that of control group; nonetheless, the MD of 0.25 mmHg was quite small in clinic and was not statistically significant. We do not think vitrectomy perform worse on IOP control.

Contrast sensitivity plays a key role in determining the capability of the visual system to handle spatial and temporal information from objects. In our review, the difference on low-contrast sensitivity between vitrectomy and non-vitrectomy group was obvious, and we had faith that vitrectomy could help patients gain a better low-contrast sensitivity.

In this meta-analysis, Vassavada (Vassavada et al. 2017) reported two cases of secondary glaucoma in vitrectomy group and zero in control group, and there was no statistical difference. No strong evidence showed that vitrectomy would increase the risk of secondary glaucoma.

Pressman SH (Pressman & Crouch 1983) even
recommended that ophthalmologists should use anterior vitrectomy with vitreoretinal instrumentation for paediatric cataract surgery to reduce the incidence of secondary glaucoma.

By this meta-analysis, cases of IOL deposit showed no difference between groups. Basti (Basti et al. 1999) reported a similar finding that younger children tend to have higher risk of forming IOL deposit. After-cataract formation could occur without the IOL, the possible mechanism might occur with large IOL in small eyes, but there was no relation with vitrectomy.

In conclusion, for congenital cataract patients, vitrectomy helps decrease the risk of VAO and reoperation after surgery, and also helps gain better low contrast sensitivity, with no other obvious drawbacks.

Author contributions

Xiu Hua Wan, Jindra Wang, Jingshang Zhang and Kai Cao conceived and designed the study; Kai Cao and Shan Shan Jin involved in database search and extracted the data; Kai Cao analysed the data; Kai Cao and Xiu Hua Wan wrote the manuscript; Mayinuer Yusufu polished the English; and Xiaohui Li, Guyu Zhu, Hailong He, Lijing Chai, Jing Li, Ying Xiong and Bingsong Wan revised the manuscript.

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Appendix 1: Search strategy

Congenital cataract AND vitrectomy [ALL]; Congenital cataract AND vitreous surgery [ALL]; Infant cataract AND vitreous surgery [ALL]; Childhood cataract AND vitrectomy [ALL]; Congenital cataract AND cataract surgery [ALL]; Pediatric cataract AND vitrectomy [ALL]; Pediatric cataract vitrectomy [ALL].

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