Systematic Review

Outcomes of paediatric cataract surgery with and without the use of trypan blue

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ABSTRACT

Objective: This systematic review was undertaken to answer the research question**:** "In children with primary cataracts, what are the outcomes (posterior continuous curvilinear capsulorhexis + posterior chamber intraocular lens implantation) of surgery when performed with and without trypan blue staining of the posterior lens capsule?"

Methods: An electronic search in six biomedical databases was conducted to identify randomised controlled trials that compared trypan blue with no stain during surgery in children 0 -16 years with primary cataracts. Titles and abstracts of studies published between 1946 and 2021 in English language were screened. Data extraction, risk of bias assessment and synthesis of findings were done by two independent reviewers, while conflicts were discussed and resolved with a third.

Results: 115 of 153 articles were screened after de-duplication. Of these, 113 were excluded while two randomised controlled trials involving 56 eyes of 42 partcipants were included in the review. The risk of bias was similar across all domains in both. Staining of the capsule led to complete posterior capsulorhexis and optimal placement of the implant in >90% of study eyes, while the control arms had 65% - 80% for both outcomes.

Conclusion: Use of trypan blue in paediatric cataract surgery probably leads to better outcomes, but more well-conducted randomised controlled trials on this important topic are needed.

Keywords: paediatric, cataract, trypan blue, systematic review

INTRODUCTION

Worldwide, cataract is the leading cause of avoidable blindness in children.(1) In the paediatric age group, some techniques of surgery that implant intraocular lenses (IOLs) primarily or secondarily require preservation of the anterior and posterior lens capsules in order to support the implant.(2) Posterior capsule opacification (PCO) and consequent vision loss, however, are a common complication if the capsule is left intact. To prevent this, the central part of the posterior lens capsule, often including the anterior vitreous gel, are removed (posterior capsulorhexis and anterior vitrectomy) while preserving the peripheral parts of the capsule.(3) This step in paediatric cataract surgery is technically challenging, and requires visualization of the posterior capsule in order to ensure an adequately sized and positioned capsulorhexis.(4) Trypan blue (5,6) is a dye used to stain the transparent, fragile, elastic lens capsule in order to improve its visualization, reduce elasticity and increase stiffness to aid in capsulorhexis creation.(7) Although the use of trypan blue is well described, a preliminary search indicated that no systematic review has been published

on its use in paediatric cataract surgery. We therefore undertook this systematic review to evaluate the evidence base regarding the effects of trypan blue as an intervention to aid posterior capsulorhexis and posterior chamber intraocular lens (PCIOL) implantation during paediatric cataract surgery. The research question was: "In children with primary cataracts, what are the outcomes (posterior continuous curvilinear capsulorhexis + PCIOL implantation) of cataract surgery when performed with and without trypan blue staining of the posterior lens capsule?"

MATERIALS & METHODS

This review is described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(8) and the protocol was registered on the Open Science Framework (OSF).(9)

Eligibility criteria

Inclusion criteria were: (i) prospective randomized controlled trials (RCTs) comparing the use of trypan blue with no stain during cataract surgery; (ii) studies conducted in children 0-16 years with congenital or developmental cataracts; (iii) studies that included primary posterior capsulorhexis with PCIOL implantation as outcomes; (iv) peer-reviewed publications in English (Table 1).

Exclusion criteria were: (i) studies involving secondary cataracts in children 0-16 years or adult cataracts; (ii) comparison of trypan blue with other ophthalmic surgical dyes; (iii) PCO prevention/treatment by means other than capsulorhexis; (iv) retrospective or non-randomised study designs.

Search strategy: Six databases were searched, namely Embase, Medline, Cochrane library, ClinicalTrials.gov, International Clinical Trials Registry Platform, and International Standard Randomised Controlled Trial Number Registry. Studies published in English between 1st January 1946 and 23rd March 2021 were retrieved using variations and combinations of these search terms: "children", "trypan blue", "paediatric cataract" and "cataract surgery". Grey literature was not searched as RCTs are not likely to be found there and peer review is not systematised. The search results were uploaded onto Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Also, the reference lists of relevant articles were manually searched to identify additional studies.

Data collection and analysis

Selection of trials: Titles and abstracts of search results were screened by two independent reviewers. Conflicts were discussed and resolved with a third reviewer. Subsequently, full-text articles of studies that fit the inclusion criteria were retrieved and screened by two reviewers according to the eligibility criteria, and reasons for exclusion documented. Eligible RCTs were assessed for methodological quality and a PRISMA flow diagram was completed to summarize the study selection process. (Figure 1)

Assessment of methodological quality: The Critical Appraisal Skills Program for Randomized Controlled Trials checklist (10) was used to assess risk of bias at both study and outcome levels. Six domains were considered and presented using a *robvis*(11) template: random sequence generation/allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. Two independent reviewers graded the trials as high, low or unclear for each domain and resolved disagreements by discussion. For unclear domains the trial authors were contacted.

Data collection: a data extraction template was developed in Microsoft Excel and piloted independently by two investigators. Data extraction from each paper was done by a single investigator and checked by a second reviewer.

Any errors or differences were discussed to arrive at a consensus.

Data synthesis: the outcome measures were reported in a format that did not allow for a meta-analysis to be done: no confidence intervals, measures of relative risk or treatment effects were reported. Very little information on statistical methods, random sequence generation and allocation was provided. We emailed the corresponding authors of each paper to seek clarification about the randomisation protocol and allocation concealment but did not receive any response. We present the results in a descriptive table and narratively.

RESULTS

A total of 153 articles were obtained from the database search while no additional records were identified from manual searching of reference lists. After de-duplication the titles and abstracts of 115 articles were screened and 113 excluded based on the eligibility criteria. Two full-text articles were retrieved and included in the review. These were two RCTs(12,13) involving a total of 56 eyes of 42 participants (See Figure 1 - PRISMA(14) flow chart). Participants' ages ranged between 0.5 and 12 years and all had either congenital or developmental cataracts. Intervention was trypan blue staining of the posterior lens capsule and both outcome measures (completeness of posterior capsulorhexis and placement of PCIOL) were reported for all participants in both trial arms (Table 2).

The risk of bias was similar in both studies across all domains, being low for outcome reporting and completeness. There was a lack of information on random sequence generation, allocation concealment and other sources of bias. Neither trial masked personnel and outcome assessors, both of which could introduce performance bias (Table 3).

Effects of the interventions

Trypan blue vs no staining for completion of posterior capsulorhexis: We found that overall, staining of the posterior lens capsule led to better surgical outcomes in all paediatric age groups. A good posterior capsulorhexis was achieved in >90% of study eyes in both studies; whereas this was so in 65% - 80% in the control groups.

Trypan blue vs no staining for PCIOL positioning: the use of trypan blue enabled PCIOL placement either in the bag or optic capture through the posterior capsulorhexis in >90% of cases. For the control groups, proper PCIOL placement was possible in 65% – 70% of eyes; and in some cases achieving a complete posterior capsulorhexis did not translate to proper PCIOL placement.

DISCUSSION

The aim of surgical management of cataracts in children is the maintenance of a clear visual axis and optical rehabilitation of the eye after removing the opaque lens. The first goal is achieved by prophylactically removing the central part of the posterior capsule intraoperatively, the second by implanting a PCIOL either in the capsular bag, or placing the IOL optic behind the posterior capsulorhexis.

The two RCTs included in this review were conducted in different settings and among different age groups (0-4 years and 5-12 years). Previous studies in children reported age as an important consideration in the decision to perform a primary posterior capsulorhexis and anterior vitrectomy (15,16). In children younger than four years, vigorous proliferation of the residual lens epithelium (from the capsule remnants) over an intact posterior capsule or anterior vitreous are responsible for the occurrence of visual axis opacity (15),(17). Older children also exhibit this response resulting in need for re-interventions to clear the visual axis. Thus, many paediatric ophthalmologists perform a primary posterior capsulorhexis and anterior vitrectomy in both younger and older children(16,18,19). This

may explain the reports of similar findings in the included RCTs despite the differences in age ranges. It is plausible that the smaller eyes of younger children may make surgery more technically challenging than the bigger eyes of older children, thus resulting in trypan blue staining giving superior results for the two outcome measures reported.

Insufficient information on the technique of randomisation could have introduced selection bias whereby the eyes that were bigger may have been selected for the intervention resulting in an easier surgery, and achievement of successful outcomes. Although it was not possible for the surgeon to be blinded as to whether trypan blue was used or not, it is very hard to conceive of a study design in which the surgeons were unaware that they were part of an RCT exploring the use of a capsule dye so it may not be possible to eliminate this potential bias. The outcome assessors, however, could certainly have been blinded in order to avoid bias. An objective way of achieving this could be taking a picture or video at the completion of capsulorhexis and IOL placement and sending to a masked assessor. Despite the limitations of the methods, evidence suggests that the outcomes (posterior capsulorhexis + optimal PCIOL placement) of paediatric cataract surgery with trypan blue staining of the posterior capsule are better than without staining.

Only one paper reported the dimensions of the posterior capsulorhexis while it was not possible to align the second outcome measures because they differed in the technique of PCIOL optic centration, so a meta-analysis was not possible. Our finding that little has been done on this topic evidenced by the small number of subjects in the two RCTs is an invitation for further research. However, to run a larger study there is need to systematically review the existing literature and that is what we did. To undertake a well-constructed search of the peer-reviewed literature is time-consuming, and it is worthwhile to report the output of that rigorous process.

Conclusion

Use of trypan blue in paediatric cataract surgery probably leads to better outcomes (completeness of posterior capsulorhexis and optimal positioning of the PCIOL), but more well-conducted RCTs on this important topic are needed.

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Table 1. PICOST framework for eligibility criteria

Population	Paediatric age group 0-16 years with congenital or developmental cataracts. Studies from any part of the world
Intervention	Cataract surgery with posterior lens capsule staining using trypan blue
Comparator	No staining of posterior lens capsule during cataract surgery
Outcome	Completeness of posterior capsulorhexis and/or Placement of IOL implant in the posterior chamber
Situation/Setting	Hospital settings
Type of study	Randomized Controlled Trials

Table 2. Characteristics of studies (RCT) included in the systematic review

Authors, (Year)		Sharma, Balasubramanya, Dada & Vajpayee (2006)	Lotfy & Abdelrahman (2017)
Methods	Study type	Randomized Controlled Trial	Randomized Controlled Trial
	Follow up	3 months	12 months
Participants	Subjects/eyes	26/35	16/21
	Age range	5 - 12 years	0.5 - 4 years
	Sex	Not reported	Males (9), Females (7)
	Eligibility	Congenital or developmental cataracts	Congenital cataracts
Intervention		Staining of posterior lens capsule with 0.1ml of 0.06% trypan blue	Staining of posterior lens capsule with 0.1ml of trypan blue (unspecified concentration)
Control		No staining of capsule	No staining of capsule
Outcomes assessed & Results	Intervention	18 eyes Completeness of posterior capsulorhexis: 17/18 (94.4%) Size of posterior capsulorhexis 4.6 ± 1.77mm PCIOL optic capture: 17/18 (94.4%)	11 eyes Completeness of posterior capsulorhexis: 10/11 (91%) PCIOL implanted in capsular bag: 10/11 (91%)
	Control	17 eyes Completeness of posterior capsulorhexis: 11/17 (64.7%) Size of posterior capsulorhexis 4.0 ± 0.93mm PCIOL optic capture - 11/17 (64.7%)	10 eyes Completeness of posterior capsulorhexis: 8/10 (80%) PCIOL implanted in capsular bag: 7/10 (70%)

Table 3. Risk of Bias Summary

Domain	**Authors (Year)** Sharma et al (2006)	Lotfy & Abdelrahman (2017)
Random sequence generation (selection bias)	Unclear	Unclear
Allocation concealment (selection bias)	Unclear	Unclear
Blinding of participants (performance bias)	Not applicable	Not applicable
Blinding of personnel (performance bias)	High	High
Blinding of outcome assessors (detection bias)	High	High
Incomplete outcome data (attrition bias)	Low	Low
Selective reporting (reporting bias) - Outcome 1	Low	Low
Selective reporting (reporting bias) - Outcome 2	Low	Low
Other sources of bias	Unclear	Unclear

Figure 1. PRISMA flow chart showing result of literature search and study selection