



Meta-analysis of visual pretreatment for the prevention of emergence delirium in children undergoing ophthalmic surgery

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Objective: To evaluate the role of visual pretreatment in preventing emergence delirium in children receiving ophthalmic surgery. **Methods:** Four randomized controlled trials were identified in four databases, and a meta-analysis was conducted using RevMan 5.3. **Results:** The meta-analysis demonstrated a significantly lower incidence of postoperative emergence delirium (risk ratio: 0.39; 95% CI: 0.31–0.49) and propofol rescue (risk ratio: 0.29; 95% CI: 0.13–0.65) but comparable modified Yale Preoperative Anxiety Scale score (mean difference: -3.66; 95% CI: -9.96 to 2.65) and incidence of adverse events in the visual pretreatment group. **Conclusion:** Visual pretreatment is effective in preventing postoperative emergence delirium in children undergoing ophthalmic surgery without significant adverse effects and can also decrease the incidence of propofol rescue.

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Keywords: children • emergence agitation • emergence delirium • general anesthesia • meta-analysis

Emergence delirium (ED) is a self-limiting condition in which those affected become inconsolable, irritable and uncooperative [1]. ED has a high incidence, ranging from 10 to 80% [2–4]. ED is reported in both children and adults; however, an increased incidence is observed in children, especially preschool children in whom anesthesia is maintained via the inhalation of sevoflurane [5]. The exact mechanism of ED has not yet been clarified, but several risk factors have been found to be associated with an increased risk of ED, including inhalational anesthesia, postoperative pain, young age, preoperative anxiety, child temperament and male sex [6–8]. Ophthalmic surgery has also been demonstrated to be an important risk factor for the occurrence of ED [9,10]. Despite numerous advancements in mechanisms and techniques, the pathogenesis of ED has not yet been sufficiently clarified [11].

ED has been found to be associated with an increased risk of several adverse events, including suture dehiscence and accidental removal of intravenous catheters resulting from a confused state and negative postoperative behavior [12]. Moreover, ED may disturb other patients present in the postanesthesia care unit and be related to long-term sequelae [11]. Currently, several anesthetics and sedatives are used for the prevention of ED [11,13–15]; however, these agents have been observed to not only prolong postanesthesia care unit stay but also cause many adverse events, such as postoperative nausea and vomiting (PONV) and breath holding [11]. Therefore, several nonpharmacological methods have been recommended to prevent the occurrence of postoperative ED in pediatric anesthesia patients [16].

Considering that the eyes are covered with ointment and patches after ophthalmic surgery, visual disturbances after surgery have been speculated to be a contributor to ED [17,18]. Thus, the use of prophylactic eye coverings the day before surgery may play a positive role in reducing the incidence of postoperative ED [17]. Recently, several studies have evaluated the efficacy and safety of visual pretreatment in the prevention of postoperative ED in children undergoing ophthalmic surgery [17,19–21]. However, due to the insufficient number of participants in most studies [17,20,21], a reliable conclusion has not yet been achieved. Therefore, the authors performed the current meta-analysis to comprehensively evaluate the efficacy and safety of visual pretreatment for the prevention of postoperative ED in children undergoing ophthalmic surgery.

Methods

The current study was designed as a systematic review and meta-analysis, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22] were used as a guide for reporting pooled results.

Literature sources

Eligible studies published up to October 2021 were independently identified by two reviewers using four databases: PubMed, Embase, the Cochrane Library and China National Knowledge Infrastructure. The terms ‘visual pretreatment’ and ‘ED’ and their analogs were used to develop the basic search query. References of included studies were also independently checked by two reviewers to identify additional studies. The detailed search strategy used in the individual databases is described in [Supplementary Table 1](#).

Selection criteria

The authors included studies based on the following characteristics: study design (randomized controlled trials fully published in English and Chinese), participants (preschool children with American Society of Anesthesiologists physical status 1 and 2 assigned to receive elective ophthalmic surgery), intervention (visual pretreatment) and outcomes (incidence of ED, modified Yale Preoperative Anxiety Scale [m-YPAS] score, incidence of propofol rescue and adverse events). The exclusion criteria were as follows: ineligible study design (e.g., case reports and comments), essential data missed and not provided by corresponding author and repeated reports of the same group.

Data extraction

Two reviewers independently extracted the relevant data from the eligible studies. Data included author names, publication year, country of origin, study duration, type of surgery, total number of participants, baseline patient characteristics (mean age, sex), details of intervention and control regimens, outcomes and details of methodological quality. For data that were reported as median and interquartile range, the authors estimated mean and standard deviation according to recognized formulas [23]. Disagreements were resolved through consulting a third reviewer. When necessary, the authors contacted the corresponding author to obtain additional information.

Definition of outcomes

The incidence of postoperative ED was regarded as the primary outcome in this meta-analysis and was defined as a peak score of ≥ 10 on the Pediatric Anesthesia ED scale [24], a score of ≥ 3 on the Watcha scale [25] or a score of ≥ 2 on the Nursing Delirium Screening Scale [26]. The level of preoperative anxiety and the incidence of propofol rescue and adverse events (recorded by individual study) were recognized as secondary outcomes. The level of preoperative anxiety was evaluated using m-YPAS [27]. The incidence of propofol rescue was defined as the proportion of patients requiring an additional dose of propofol for the treatment of severe agitation [17].

Quality assessment

Two independent reviewers used the Cochrane risk of bias tool [28] to assess the methodological quality of individual eligible studies based on seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. According to the criteria of the Cochrane tool, the bias risk of each item was labeled low, unclear or high.

Statistical analysis

Pooled estimates of categorical and continuous variables were expressed as risk ratio and mean difference, respectively. A 95% CI was used for each effect size. Cochran's Q statistic [29] was used to qualitatively assess statistical heterogeneity, and the I^2 statistic [30] was used to quantify the level of statistical heterogeneity across studies. Nevertheless, the authors used a random effects model [31] to perform all statistical analyses regardless of the level of heterogeneity because variations between studies could not be ignored in real settings. The authors did not draw a funnel plot to inspect publication bias because an insufficient number of eligible studies were identified [32]. A $p < 0.05$ was considered to indicate a statistically significant difference. The authors used RevMan 5.3 software (Cochrane Collaboration, London, UK) to perform statistical analysis [33].

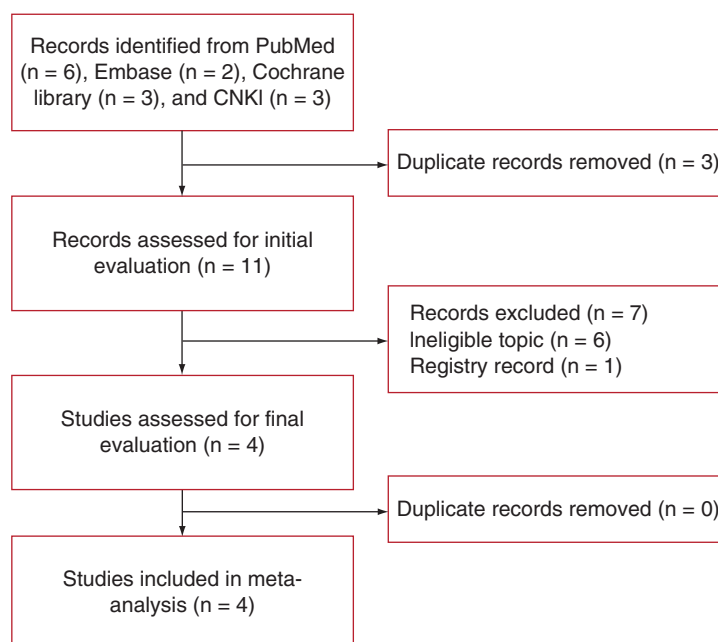


Figure 1. Flowchart of study retrieval and selection.

Results

Study retrieval & selection

After initially searching four electronic databases, a total of 14 records were identified. The authors subsequently used literature management software (EndNote, Clarivate Analytics) to remove three duplicate records. Next, the authors excluded seven ineligible studies after carefully checking the titles and abstracts of the remaining 11 studies. At the final stage of the eligibility evaluation, no ineligible study was identified based on full texts. Finally, four studies involving 679 preschool children were included in the meta-analysis [17,19–21]. The process of study retrieval and selection is displayed in Figure 1.

Basic characteristics of the included studies

Of the four included studies, one was published in 2018 [17] and three were published in 2021 [19–21]. All included studies [17,19–21] were performed in China. The four included studies involved different types of surgeries. Three studies [17,19,21] were designed with two arms and one study [20] was designed with three arms. The sample size of the individual studies ranged from 95 to 279, with a total number of 679. The basic characteristics of the included studies are summarized in Table 1.

Quality assessment of included articles

The Cochrane risk of bias tool was applied to assess the methodological quality of the four included articles, and the risk of bias summary is shown in Figure 2. Results suggested that all included studies [17,19–21] correctly generated a random sequence; however, only one study [17] reported the details of allocation concealment with the appropriate method. The authors labeled all included studies [17,19–21] with low risk of bias in performance bias because behaviors of participants and personnel could not bias outcomes. With regard to the remaining four items, the four included studies were deemed to have a low risk of bias. Overall, the methodological quality of the included studies was moderate to high.

Meta-analysis incidence of ED

All included studies [17,19–21] reported the incidence of postoperative ED. Based on results of the statistical heterogeneity examination, it was observed that there was no obvious statistical heterogeneity in the incidence of postoperative ED between the visual pretreatment and standard control groups ($I^2 = 0\%$; $p = 0.96$). The results revealed that the estimate of the incidence of postoperative ED in the visual pretreatment and standard control groups was 0.39 (95% CI: 0.31–0.49). In summary, the difference in the incidence of postoperative ED between both groups was statistically significant (21.43 vs 55.79%; $Z = 8.09$; $p < 0.001$) (Figure 3). In addition, one

Table 1. Basic characteristics of included studies.													
Study	Country	Study duration	Condition	Group	Sample size (male/female)	Age, years	m-YPAS score	ED	Propofol rescue	PONV	Breath holding	SpO ₂ <95%	Ref.
Lin, et al.	China	01/2016–07/2017	Cataract surgery	VP	88 (47/42)	5	37.9 ± 20.4	15	4	0	1	0	[17]
				C	90 (51/39)	4.8	39.0 ± 19.2	40	14	0	1	0	
Wei, et al.	China	01/2020–12/2020	Strabismus surgery	VP	46 (25/21)	4.81	n.a.	9	3	2	2	1	[21]
				C	49 (26/23)	5.24	n.a.	27	11	4	2	1	
Dong, et al.	China	08/2019–07/2020	Mixed	VP	133 (73/60)	4.84	36.36 ± 13.47	38	n.a.	n.a.	n.a.	n.a.	[19]
				C	146 (76/70)	4.8	45.45 ± 16.84	103	n.a.	n.a.	n.a.	n.a.	
Liu, et al.	China	06/2019–07/2020	Bilateral chalazion resection	VP	41 (22/19)	3.4	35 ± 13	4	n.a.	0	n.a.	n.a.	[20]
				Dex	43 (24/19)	3.5	32 ± 9	5	n.a.	0	n.a.	n.a.	
				C	43 (23/20)	3.7	35 ± 10	13	n.a.	0	n.a.	n.a.	
C: Control; Dex: Dexmedetomidine; ED: Emergence delirium; m-YPAS: Modified Yale Preoperative Anxiety Scale; n.a.: Not available; PONV: Postoperative nausea and vomiting; VP: Visual pretreatment.													

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong, <i>et al.</i> , 2021	+	?	+	+	+	+	+
Lin, <i>et al.</i> , 2018	+	+	+	+	+	+	+
Liu, <i>et al.</i> , 2021	+	?	+	+	+	+	+
Wei, <i>et al.</i> , 2021	+	?	+	+	+	+	+

Figure 2. Risk of bias assessment of the studies included in the meta-analysis.

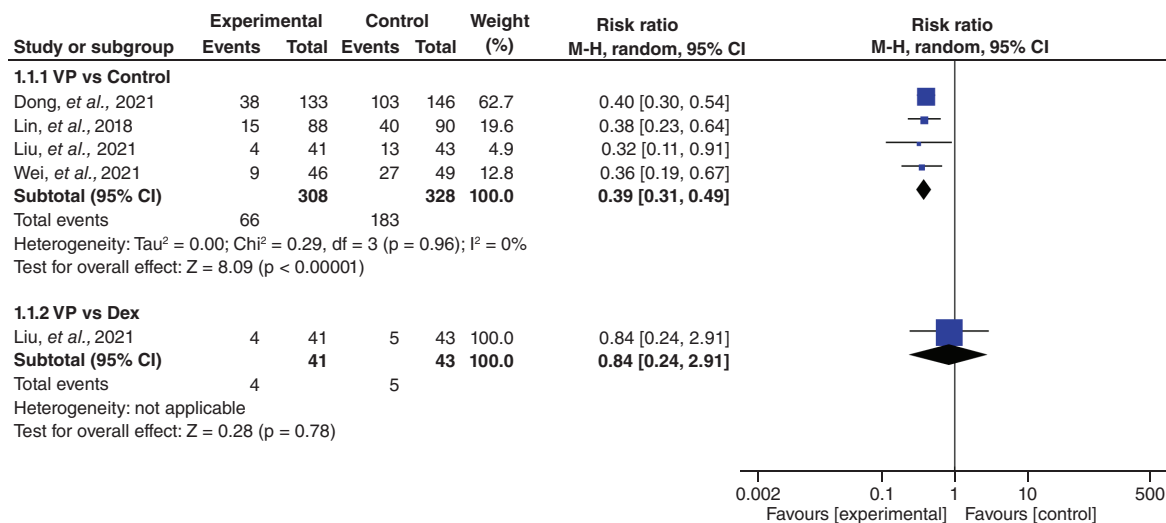


Figure 3. Forest plot of meta-analysis of the incidence of emergence delirium.

Dex: Dexmedetomidine; VP: Visual pretreatment; CI: confidence interval; M-H: Mantel-Haenszel.

study investigated the comparative efficacy of visual pretreatment versus dexmedetomidine, and the meta-analysis suggested no statistical difference in terms of incidence of postoperative ED (risk ratio: 0.84; 95% CI: 0.24–2.91; $p = 0.78$).

Meta-analysis of m-YPAS score

The authors analyzed the differences in m-YPAS score between the visual pretreatment and standard control groups (Figure 4). Based on results of the heterogeneity examination, obvious statistical heterogeneity was detected in m-YPAS score between the two groups ($I^2 = 81\%$; $p = 0.005$). The results revealed that the pooled effect of the m-YPAS score in both groups was -3.66 (95% CI: -9.96 to 2.65). In summary, the m-YPAS score in the visual

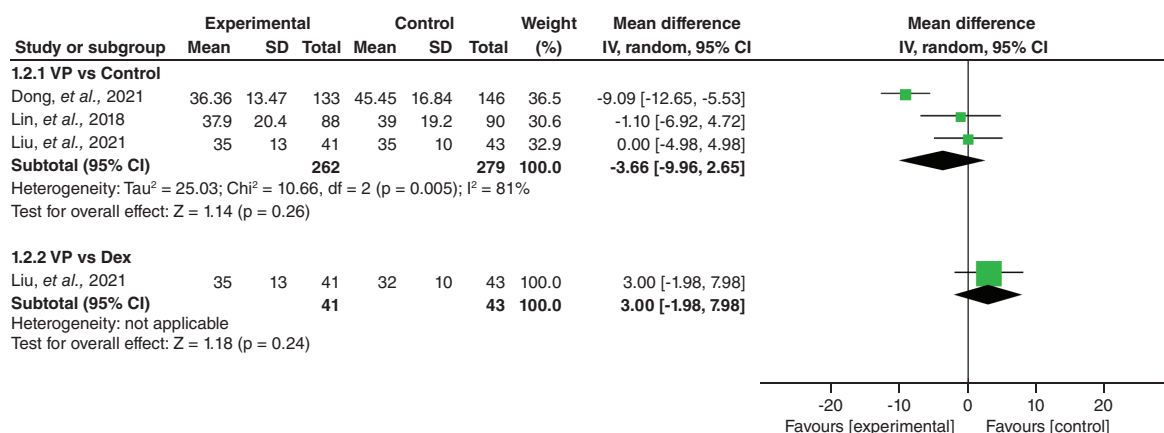


Figure 4. Forest plot of meta-analysis of modified Yale Preoperative Anxiety Scale scores.

Dex: Dexmedetomidine; VP: Visual pretreatment; IV: Inverse Variance.

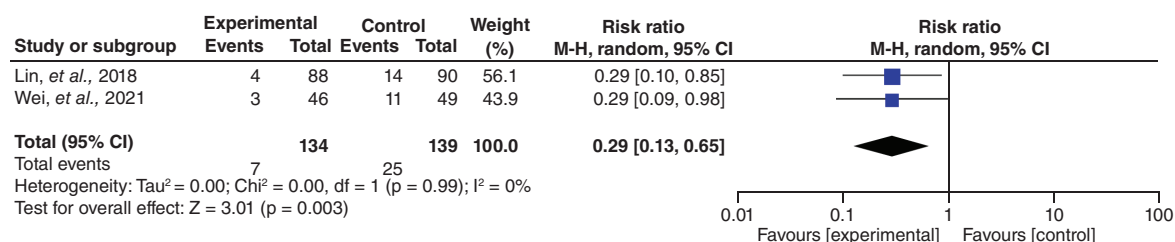


Figure 5. Forest plot of meta-analysis of incidence of propofol rescue.

M-H: Mantel-Haenszel; CI: confidence interval.

pretreatment group was numerically lower than that observed in the standard control group, although the difference was not statistically significant ($Z = 1.14$; $p = 0.26$). The meta-analysis also suggested no statistical difference in terms of m-YPAS score between the visual pretreatment and dexmedetomidine groups (mean difference: 3.00; 95% CI: -1.98 to 7.98; $p = 0.24$).

Meta-analysis of incidence of propofol rescue

The authors compared and analyzed differences in the incidence of propofol rescue between the visual pretreatment and standard control groups (Figure 5). Statistical heterogeneity examination revealed no significant heterogeneity ($I^2 = 0\%$; $p = 0.99$), and results of the meta-analysis suggested a significantly lower incidence of propofol rescue in the visual pretreatment group compared with the standard control group (5.22 vs 17.99%; risk ratio: 0.29; 95% CI: 0.13–0.65; $Z = 3.01$; $p = 0.003$).

Meta-analysis of incidence of adverse events

Among included studies, three studies [17,20,21] reported the incidence of PONV, and two studies [17,21] reported the incidence of breath holding and $SpO_2 < 95\%$. Statistical heterogeneity examinations did not detect obvious heterogeneity in terms of the incidence of PONV (heterogeneity not applicable), breath holding ($I^2 = 0\%$; $p = 0.98$) or $SpO_2 < 95\%$ (heterogeneity not applicable). Results of the meta-analyses revealed a comparable incidence between the visual pretreatment and standard control groups in terms of PONV (1.14 vs 2.20%), breath holding (2.24 vs 2.16%) and SpO_2 (0.75 vs 0.72%) (Figure 6).

Discussion

Summary of main findings

ED is commonly observed in children undergoing pediatric anesthesia, especially preschool children maintained via the inhalation of sevoflurane [11]. Nonpharmacological methods have been suggested to reduce the incidence of postoperative ED because anesthetics and sedatives have been found to be associated with an increased risk of

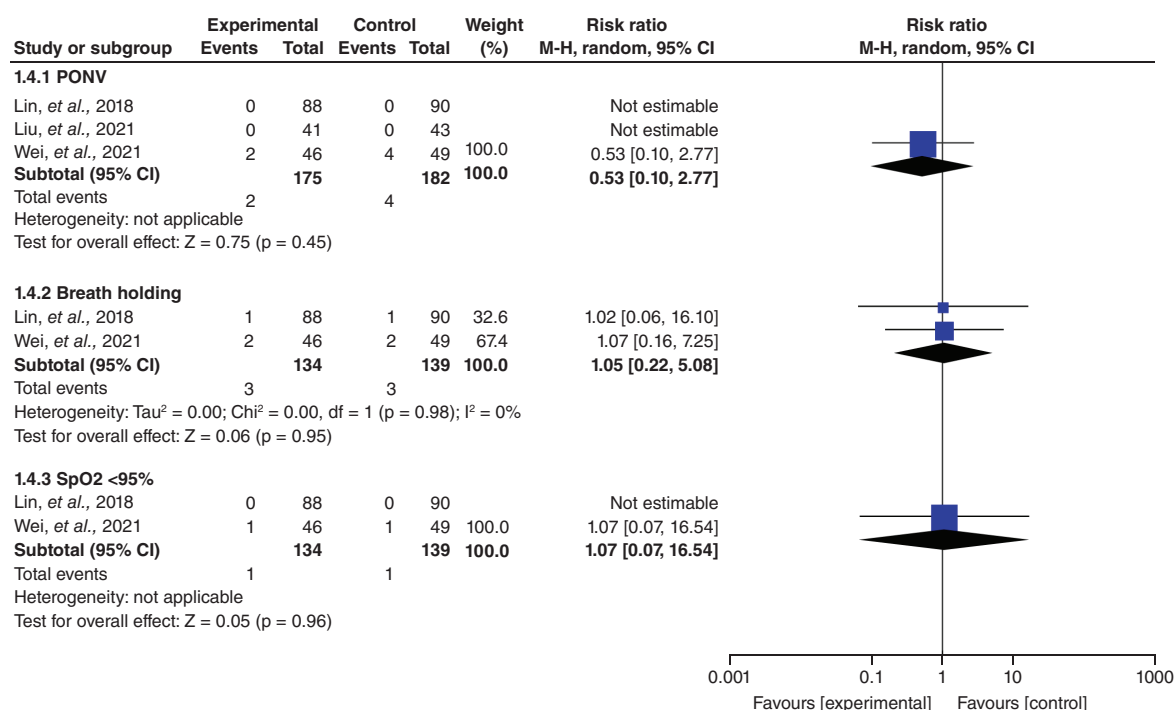


Figure 6. Forest plot of meta-analysis of incidence of adverse events.

PONV: Postoperative nausea and vomiting; SPO₂: pulse oxygen saturation; CI: confidence interval; M-H: Mantel-Haenszel.

many undesirable side effects [16]. In the present meta-analysis of four eligible studies, the authors demonstrated that, as a nonpharmacological method, visual pretreatment is effective in decreasing the incidence of postoperative ED and propofol rescue without significant adverse effects in children undergoing ophthalmic surgery.

Potential reasons for results

Application of eye ointment and an eye patch after ophthalmic surgery may play a critically important role in the occurrence of postoperative ED [17]. Owing to immature neural development, visual disturbance has been considered to be the main reason for the high incidence of postoperative ED [34], and therefore visual pretreatment using an eye patch on the eyes the day before surgery has been speculated to have a positive impact on the occurrence of postoperative ED in children undergoing ophthalmic surgery [17,18]. All studies [17,19–21] included in the current meta-analysis consistently revealed a beneficial effect of visual pretreatment with regard to reducing the incidence of postoperative ED. The authors' meta-analysis further demonstrated the beneficial role of visual pretreatment in the prevention of postoperative ED through increasing statistical power after combining the results of individual studies [33]. It should be noted that the use of visual pretreatment is also comparable to dexmedetomidine in the prevention of postoperative ED [20]. Moreover, the authors' meta-analysis suggested that visual pretreatment significantly reduces the proportion of patients requiring propofol rescue, which further confirms the preventive efficacy of visual pretreatment for postoperative ED in children undergoing ophthalmic surgery.

Preoperative anxiety has been speculated to be associated with the occurrence of postoperative ED in children undergoing ophthalmic surgery [35]. To date, several studies have investigated the relationship between preoperative anxiety and the incidence of postoperative ED [11]; however, conflicting results were reported [36–38]. Of the three included studies [17,19,20] that reported preoperative anxiety, only one [19] reported a significant reduction in m-YPAS score in the visual pretreatment group. In this meta-analysis, the authors detected a greater reduction in m-YPAS score in the visual pretreatment group, although no statistical difference was observed. Moreover, Lin *et al.* suggested that preoperative anxiety was still an independent risk factor for postoperative ED [17], although preoperative anxiety scores were comparable between both groups studied. Thus, it is necessary to further clarify whether preoperative anxiety is related to the occurrence of postoperative ED in children undergoing ophthalmic surgery.

Table 2. Detailed information of interventions used in each eligible study.

Study	Group	Details of regimen	Ref.
Lin, <i>et al.</i> , 2018	VP	Prophylactic treatment with eye patch by covering the eye to be operated on for at least 3 h the day before surgery	[17]
	C	Programmed explanation [†]	
Wei, <i>et al.</i> , 2021	VP	Prophylactic treatment with eye patch by covering the eye to be operated on for 1 h 3 days before surgery	[21]
	C	Programmed explanation [†]	
Dong, <i>et al.</i> , 2021	VP	Prophylactic treatment with eye patch by covering the eye to be operated on the day before surgery	[19]
	C	Programmed explanation [†]	
Liu, <i>et al.</i> , 2021	VP	Prophylactic treatment with eye patch by covering the eye to be operated on 2 days before surgery	[20]
	Dex	0.5 µg/kg for 15 min	
	C	Programmed explanation [†]	

[†]Discussion regarding how the surgery will be performed and what will happen after the surgery using words and cartoons.

C: Control; Dex: Dexmedetomidine; VP: Visual pretreatment.

As mentioned previously, because pharmacological interventions are associated with a higher risk of adverse effects, several nonpharmacological methods have been developed and recommended for the alleviation of ED [16]. In the current meta-analysis, the authors detected a comparable incidence of PONV, breath holding and SpO₂ <95% between the visual pretreatment and standard control groups, which further demonstrates the safety profile of visual pretreatment in practice.

Limitations & strengths

Certainly, the authors' meta-analysis has some limitations that should be further explained. First, as is the case with some studies, most included studies had a relatively insufficient sample size, which may introduce choice, biasing the authors' results. Second, only four eligible studies were included in this meta-analysis, which might weaken the robustness and credibility of the authors' findings. Third, although all included studies used visual pretreatment regimens as an intervention, a variety of components were used in the design of the visual pretreatment protocols (Table 2). Because of the insufficient number of eligible studies, the authors could not conduct subgroup analysis to eliminate the possible impact of components on pooled results. Fourth, various ophthalmic surgeries were utilized in the included studies, which may also introduce bias, negatively affecting the authors' results. Fifth, different scales were used to identify ED in all included studies, and it is impossible to eliminate the impact of scales on the pooled results. Sixth, all studies included in this meta-analysis were conducted in China, and therefore the authors' findings should be cautiously interpreted in different clinical settings. Seventh, the formal protocol of the present meta-analysis was not registered on a public platform; however, the authors performed this meta-analysis in strict accordance with the Cochrane handbook. In spite of these limitations, the authors' study has two major advantages: it is the first meta-analysis to systematically evaluate the efficacy and safety of visual pretreatment for the prevention of postoperative ED in children undergoing ophthalmic surgery, and a systematic literature search was utilized to significantly reduce the risk of reporting bias.

Conclusion

A total of four relevant studies were included in this meta-analysis to systematically evaluate the clinical efficacy and safety of visual pretreatment for the prevention of postoperative ED. In summary, the results suggested that visual pretreatment can effectively reduce the incidence of postoperative ED and propofol rescue and can significantly reduce preoperative anxiety. In addition, visual pretreatment has a desirable safety profile. We therefore suggest the use of visual pretreatment in clinical practice, although more studies are required to clarify the association between preoperative anxiety and postoperative ED.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2022-0037

Author contributions

D She designed the study, wrote the original draft and reviewed and edited the manuscript. Z-Y Wang designed the study, wrote the original draft and reviewed and edited the manuscript. F Wu reviewed and edited the manuscript as well as English usage. Y-Q Zhang reviewed and edited the manuscript. Q Ao supervised and reviewed the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Summary points

- Emergence delirium (ED) is a self-limiting condition in which those affected become inconsolable, irritable and uncooperative.
- ED has a high incidence, especially in children.
- Pediatric ophthalmic surgery has also been demonstrated to be an important risk factor for the occurrence of ED.
- A significantly high risk of adverse events limits the clinical application of anesthetics and sedatives for the prevention of ED.
- Prophylactic eye coverings the day before surgery may play a positive role in reducing the incidence of postoperative ED, as visual disturbances after surgery have been speculated to be a contributor to ED.
- Visual pretreatment is considered to be an easy-to-use and inexpensive nonprophylactic eye covering strategy.
- Several original studies investigating the role of visual pretreatment in the prevention of ED in children undergoing ophthalmic surgery have reported conflicting findings.
- This meta-analysis included four eligible randomized controlled trials and suggested that visual pretreatment significantly lowers the incidence of postoperative ED and propofol rescue.
- However, no statistical difference was observed between visual pretreatment and control strategies in terms of modified Yale Preoperative Anxiety Scale score and incidence of adverse events.

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