Penehyclidine mitigates intraoperative oculocardiac reflex and postoperative nausea and vomiting in the patients with strabismus surgery: a prospective, randomized, double-blinded comparison

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Abstract

Background

PONV is one of the most frequent complications following anesthesia and strabismus surgery. Penehyclidine, an anticholinergic, is widely and preoperatively used for reducing glandular secretion in patients. This study investigated the effect of penehyclidine on PONV in strabismus surgery.

Methods

In this prospective, randomized, and double-blinded study, patients of strabismus surgery under general anesthesia were randomly assigned to either penehyclidine (n = 114) or normal saline (NS, n = 104) groups. Penehyclidine was administrated immediately after anesthesia induction, and patients treated with NS served as controls. PONV was investigated within 48 h after surgery. Intraoperative OCR was also recorded.

Results

Compared with NS controls, penehyclidine significantly reduced PONV incidence [30.7% vs. 54.8%, P < 0.001] and mitigated PONV severity as indicated by severity scoring (P < 0.001). When stratified by gender and age, the reduction of PONV incidence following penehyclidine treatment was found significant in all adult patients and male underaged patients. Unexpectedly, penehyclidine also significantly reduced OCR incidence [57.9% vs. 77.9%, P < 0.01] and mitigated OCR severity which indicated by requirement of atropine to rescue [77.3% vs. 90.1%, P < 0.05]. Moreover, penehyclidine did not significantly change anesthesia recovery time, facial flushing and drowsiness occurrence compared to NS controls.

Conclusions

Penehyclidine administration after anesthesia induction significantly attenuated intraoperative OCR and PONV in strabismus surgery patients.

Trial registration

ClinicalTrials.gov (NCT04054479). Registered July 19, 2019, https://www.clinicaltrials.gov/ct2/show/NCT04054479?id=NCT04054479&draw=2&rank=1

Background

Strabismus surgery is a common ophthalmic surgical procedure, especially in pediatric patients. Intraoperative oculocardiac reflex (OCR) and postoperative nausea and vomiting (PONV) are the most frequent complications following anesthesia and strabismus surgery (1, 2). OCR, also known as the Aschner reflex, is defined as a decrease in heart rate (HR) by greater than 20% following eyeball pressure or traction of the extraocular muscles (3). The incidence of OCR ranges from 14 ~ 90% during strabismus.
surgery (4). The reflex commonly results in bradycardia and associates with reduced arterial pressure, arrhythmia, asystole, and even cardiac arrest (5). As for PONV, the incidence has been shown as high as 38~68.2% in pediatric and 45.2% in adult patients with strabismus surgery (6–9). Besides increasing unpleasant experience and delaying discharge, PONV can lead to postoperative complications that include fluid and electrolyte imbalances, suture tension, esophageal tear, increased intracranial pressure, and pulmonary aspiration (1, 10). Therefore, both OCR and PONV remain main concerns in strabismus surgery (11).

Penehyclidine is an anticholinergic agent with an elimination half-life over 10 h. As described a selective blocker of type 1 and type 3 muscarinic acetylcholine receptors, penehyclidine is widely used in preoperative medication mainly for reducing glandular secretion (12, 13). Moreover, penehyclidine is used to reverse organic phosphorus pesticide poisoning (12). Interestingly, Type 3 and type 5 muscarinic acetylcholine receptors have been shown playing roles in the development of motion sickness, a risk factor of PONV (14). Moreover, type 1 muscarinic acetylcholine receptors present at high levels in vestibular system, and anticholinergics block cholinergic transmission from the vestibular nuclei to higher CNS centers as well as from the medullary reticular formation to the vomiting center(15). When taken into account that the muscarinic acetylcholine receptors are involved in the development of PONV through multiple mechanisms, it is possible, therefore, that penehyclidine may play a role in preventing patients from PONV in strabismus surgery. As penehyclidine weakly blocks type 2 muscarinic acetylcholine receptors, its possible effect on OCR during strabismus surgery is also worth exploring.

This prospective, randomized, and double-blinded study was designed to identify whether penehyclidine functions as an effective protector against intraoperative oculocardiac reflex and postoperative nausea and vomiting in the patients with strabismus surgery.

**Methods**

**Patients**

This study was prospectively approved by the Human Research Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (#2019-SR-238) and a written informed consent was obtained from patients or their legal guardians. A total of 228 consecutive patients aged 3~65 years for strabismus surgery under general anesthesia with American Society of Anesthesiologists Physical Statuses I and II were enrolled into the present investigation. All methods were performed in accordance with the relevant guidelines and regulations. This manuscript adheres to the applicable CONSORT 2010 guidelines. The patients with obvious vital organ diseases, motion sickness, previous PONV history, smoking, medication with steroids or proton pump inhibitors, or did not cooperate with the investigation were excluded. All cases were prospectively and randomly divided into penehyclidine group and normal saline group. The primary outcome for our study was the effect of penehyclidine on the incidence of nausea and vomiting during the first 48 hours postoperatively. The secondary outcome was the possible effect of penehyclidine on the occurrence of OCR during surgery.
Study protocol

Anesthesia induction. After routine preoperative fast for over 6 ~ 8 h, patients were transferred to the operating room and monitored with ECG, SpO$_2$ and non-invasive blood pressure. After establishing venous access, patients were infused with lactated Ringer's solution at a rate of 10 ~ 15 mL·kg$^{-1}$·hr$^{-1}$ throughout anesthesia and operation. Anesthesia of all the patients were induced with propofol 1.5 ~ 2.5 mg·kg$^{-1}$ and fentanyl 5.0 µg·kg$^{-1}$. Cisatracurium 0.15 mg·kg$^{-1}$ was used to paralyze the patient to facilitate tracheal intubation. No midazolam or inhalational anesthetics were used. Lungs were ventilated with a tidal volume of 7 ~ 10 mL·kg$^{-1}$ and a frequency of 10 ~ 22 times per minutes to maintain end tidal CO$_2$ at the level of 35 ~ 40 mmHg. The fraction of inspired oxygen was maintained at 60%.

Anesthesia maintenance. The anesthesia was maintained with infusion of propofol at a rate of 60 ~ 200 µg·kg$^{-1}$·min$^{-1}$ and remifentanil at a rate of 0.1 ~ 0.15 µg·kg$^{-1}$·min$^{-1}$. No muscle relaxant was further added.

Anesthesia recovery. Propofol and remifentanil infusion were discontinued as surgery completed and all patients were spontaneously recovered without use of neostigmine and atropine to reverse residual muscle relaxant. During the recovery period, patients who complained of severe pain were treated with parecoxib at a dose of 1.0 mg·kg$^{-1}$ with an upper limit to 40 mg and patient who complained of severe PONV was rescued by granisetron at a dose of 50 µg·kg$^{-1}$ with an upper limit to 3.0 mg.

Penehyclidine treatment. Simple randomization was employed by lottery method and the patients were randomly allocated into penehyclidine or normal saline groups with equal chance. Penehyclidine was administrated immediately after anesthesia induction, and the equal volume of normal saline served as controls. Penehyclidine was administrated with the dosage of 10 µg·kg$^{-1}$ and with an upper limit to 0.5 mg. The lots were prepared by a resident and penehyclidine or normal saline was given by an attending doctor according to the lot drawn from the envelope. Patients were unaware of the treatment groups.

Postoperative nausea and vomiting (PONV)

Nausea and vomiting were investigated within 48 h after strabismus surgery by a resident who was blinded to the treatment of penehyclidine or normal saline. The occurrence of PONV was recorded by interviewing with the patients or the legal guardians of children patients at 2, 6 and 24 h after surgery in the hospital and by a telephone call after discharge (48 h). The severity of PONV was scored using a numeric rank scoring system according to previous method (16). The scoring system was composed of four levels of PONV: 0, no nausea or vomiting; 1, nausea but no vomiting; 2, vomiting once or twice; 3, vomiting on more than two occasions. PONV was expressed as incidence (percentage) of patients.

The patients with severe (scored at 3) and intolerable PONV were treated with antiemetics granisetron at a dose of 50 µg·kg$^{-1}$ with an upper limit to 3.0 mg.
Oculocardiac reflex (OCR)

OCR was defined as a decrease in heart rate (HR) by greater than 20% following eyeball pressure or traction of extraocular muscles\(^{(3)}\). Once OCR was observed, the operation was paused to relieve OCR, and the operation restarted when heart rate returned to baseline value. If HR did not recover in 30 s or severe bradycardia (HR < 60 bpm for aged 3 ~ 7 years, and < 50 bpm for over 7 years old) sustained for over 10 s, intravenous atropine \(10\mu\text{g}·\text{kg}^{-1}\) with an upper limit to 0.5 mg was administered.

Sample size estimation and statistical analysis

Pre-study power analysis indicated that 94 cases in each group were required based on 50% incidence of PONV following strabismus surgery without antiemetics and 30% with penehyclidine (\(\alpha = 0.05\) and \(1-\beta = 0.8\)). With an anticipation of 10% dropout, at least 105 cases in each group were required for randomization.

Data analysis was performed using IBM SPSS software, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables conforming to normal distribution were expressed as mean ± standard deviation and Student’s two-tailed unpaired \(t\)-test was used for comparison between two groups. Non-normal continuous variables were expressed as median (interquartile range, IQR) and Mann-Whitney U test was used for comparison between two groups. Categorical variables were expressed as number and percentage, and analyzed by Fisher's exact test. For ranked data, Mann-Whitney U test was used for comparison between two groups. Subgroup analysis was performed to explore whether the anti-emetic effect of penehyclidine is influenced by gender and age. Univariable logistic regression was used to identify the potential risk factors that might affect PONV incidence, and the factors with \(P < 0.10\) were included in the multivariable logistic regression. A \(P\) value < 0.05 was considered as significant.

Results

1. Patients in the investigation

From July 20, 2019 to November 1, 2019, 228 patients were randomly allocated to penehyclidine or normal saline groups. Among them, 10 patients dropped out due to lost contact or due to using inhalation anesthesia induction in pediatric patients who did not cooperate with intravenous induction. Therefore, 218 patients were finally analyzed. The consort flow diagram was shown in Fig. 1.

Between penehyclidine and normal saline control groups, the patients showed comparable general characteristics, including age, gender, body weight, body height, duration of surgery, duration of anesthesia, unilateral or bilateral operation of eye, and numbers of operated muscles (Table 1).
Table 1  
General characteristics of patients

| Parameters                      | Normal saline (n = 104) | Penehyclidine (n = 114) | P value |
|---------------------------------|-------------------------|-------------------------|---------|
| Age (year)                      | 10 (11)                 | 11 (14)                 | 0.398   |
| Gender (Male/Female)            | 61/43                   | 57/57                   | 0.222   |
| Body weight (kg)                | 42.5 (33.4)             | 47.5 (33.3)             | 0.412   |
| Body height (cm)                | 150 (43)                | 155 (35)                | 0.656   |
| Duration of surgery (min)       | 28 (16)                 | 30 (16)                 | 0.668   |
| Duration of anesthesia (min)    | 64 (17.3)               | 63.5 (20)               | 0.631   |
| Unilateral/bilateral operation  | 18/86                   | 19/95                   | 1.000   |
| Number of operated muscles      | 3 (2)                   | 3 (2)                   | 0.753   |

Age, body weight, body height, duration of surgery, duration of anesthesia and number of operated muscles are expressed as medium (IQR), and compared by Mann-Whitney U test between normal saline group and penehyclidine group. Gender is expressed as numbers of male/female patients and Unilateral/bilateral operation is expressed as numbers of the respective patients, and Fisher's exact test was used for comparison between normal saline group and penehyclidine group.

2. Administration of penehyclidine reduces overall incidence of PONV in strabismus surgery

To investigate the effect of penehyclidine on PONV in patients with strabismus surgery, we recorded the occurrences of PONV within 48 h after surgery. As shown in Fig. 2A, PONV incidence was 30.7% (35/114) in patients treated with penehyclidine and 54.8% (57/104) in patients treated with normal saline. Therefore, penehyclidine significantly reduced PONV incidence by 44.0% (P < 0.001).

3. Administration of penehyclidine mitigates the severity of PONV in strabismus surgery

The effect of penehyclidine on the severity of PONV after strabismus surgery was analyzed. The severity of PONV was scored using a numeric rank scoring system which ranging from 0 to 3, wherein 0 represented no nausea and no vomiting and 3 represented vomiting on more than two occasions (16). Notably, penehyclidine administration significantly mitigated the severity of PONV within 48 h after surgery as compared to normal saline controls (P < 0.001) (Fig. 2B).

4. The anti-PONV effect of penehyclidine over time

4.1 PONV shows high incidence within 6 h after strabismus surgery
To observe the dynamic change of PONV after strabismus surgery, PONV incidence during 0 ~ 2, 2 ~ 6, 6 ~ 24 and 24 ~ 48 h postoperative periods were analyzed. In normal saline control group, 40.4% (42/104) patients suffered from PONV during 0 ~ 2 h and the incidence remained as high as 35.6% (37/104) during 2 ~ 6 h after surgery. Interestingly, PONV incidence robustly and significantly decreased during the periods of 6 ~ 24 h (8.7%, 9/104) and 24 ~ 48 h (1.0%, 1/104) after surgery, respectively, compared to that during 0 ~ 2 h after surgery (P<0.001) (Fig. 3). The data suggest that the PONV is prominently present within 6 h post-strabismus surgery.

4.2 Penehyclidine shows pronounced protection from PONV within 6 h after strabismus surgery

The effect of penehyclidine on PONV incidence over time postoperatively were similarly observed. It was found that following penehyclidine administration, the incidences of PONV were 25.4%, 18.4%, 5.3% and 0% in the periods of 0 ~ 2, 2 ~ 6, 6 ~ 24 and 24 ~ 48 h after strabismus surgery. Notably, penehyclidine administration significant reduced PONV incidence by 37.0% and 48.2% in the periods of 0 ~ 2 and 2 ~ 6 h after surgery, respectively, when compared to the time-matched normal saline-treated controls (P<0.05 or 0.01) (Fig. 3). No significance of PONV incidence was observed after 6 h post-surgery between penehyclidine and its normal saline control group. The data suggest a pronounced protection of penehyclidine from PONV within 6 h after strabismus surgery.

5. The anti-emetic effect of penehyclidine is affected by gender and age of patients

To explore whether the anti-emetic effect of penehyclidine is influenced by gender and age, patients were divided into 4 subgroups according their genders (male and female) and ages (underage of 3 ~ 17 and adult of 18 ~ 65 years old). As shown in Fig. 4, penehyclidine significantly reduced the incidence of PONV in male patients aged 3 ~ 17 and 18 ~ 65 years old, respectively, when compared to the age- and gender-matched normal saline controls (P<0.01 or 0.05). Female patients aged 18 ~ 65 years old also showed significantly reduced PONV incidence following penehyclidine administration compared to their gender and age-matched normal saline controls (P<0.05). No difference was found in female patients aged 3 ~ 17 years old. The data indicate that gender and age impacts the penehyclidine-induced protection from PONV after strabismus surgery.

6. Penehyclidine independently reduces PONV risk in patients with strabismus surgery

To exclude the confounding factors those potentially interfere the anti-PONV effect of penehyclidine, logistic regression analysis was conducted. Multivariable logistic regression showed that operation with 4 ~ 6 muscles independently increased PONV risk in strabismus surgery (Odds Ratio, 3.553; 95% confidence interval, 1.909 ~ 6.615; P<0.001). Gender, age, occurrence of OCR, duration of surgery, and duration of anesthesia were not associated with PONV in this study. Most importantly, the logistic
regression showed that penehyclidine was an independent protective factor (Odds Ratio, 0.330; 95% confidence interval, 0.178 ~ 0.609; $P < 0.001$) that reduced PONV risk in patients with strabismus surgery (Table 2).

### Table 2

Univariable and multivariable logistic regression analysis

| Variables                  | Univariable Analysis | Multivariable Analysis |
|----------------------------|----------------------|------------------------|
|                            | Odds Ratio (95% CI)  | P value                | Odds Ratio (95% CI)  | P value    |
| Gender                     |                      |                        |                        |            |
| 1.146 (0.668 ~ 1.965)      | 0.621                |                        |                        |            |
| Age (years)                |                      |                        |                        |            |
| 18 ~ 65                    | 0.540 (0.288 ~ 1.011)| 0.054                  | 0.750 (0.377 ~ 1.489)  | 0.410      |
| EOM operated (n)           |                      |                        |                        |            |
| 1 ~ 3                      | -                    | -                      | -                      |            |
| 4 ~ 6                      | 3.344 (1.906 ~ 5.868)| < 0.001                | 3.553 (1.909 ~ 6.615)  | < 0.001    |
| Oculocardiac reflex        | 2.224 (1.216 ~ 4.068)| 0.009                  | 1.558 (0.807 ~ 3.006)  | 0.186      |
| Penehyclidine              | 0.365 (0.210 ~ 0.636)| < 0.001                | 0.330 (0.178 ~ 0.609)  | < 0.001    |
| Duration of surgery (min)  | 1.012 (0.991 ~ 1.035)| 0.263                  |                        |            |
| Duration of anesthesia (min)| 1.007 (0.991 ~ 1.022)| 0.394                  |                        |            |

Univariable logistic regression was performed first and the factors with $P < 0.10$ were included in the multivariable logistic regression. As a result, age, extraocular muscles operated, occurrence of oculocardiac reflex and use of penehyclidine were selected for multivariable logistic regression. CI, confidence interval; EOM, extraocular muscles.

7. Administration with penehyclidine reduces incidence and severity of oculocardiac reflex (OCR) during strabismus surgery

OCR, defined as a decrease in heart rate by greater than 20% following eyeball pressure or traction of extraocular muscles, is a frequent and serious complication during strabismus surgery. Interestingly, it was found that a 25.7% lower OCR incidence in the patients received penehyclidine administration (66/114) than that in the normal saline control patients (81/104) during strabismus surgery ($P < 0.01$) (Fig. 5A).
Severe OCR, as indicated by sustained decrease of heart rate greater than 20% of basal value or severe bradycardia, may cause hypotension and even cardiac arrest. Atropine is usually used to rescue severe OCR. Notably, significant reduction of OCR patients needing atropine rescue was observed in penehyclidine group (51/66) compared to that of OCR patients in normal saline group (73/81) ($P<0.05$) (Fig. 5B). The data indicate that penehyclidine administration significantly mitigated the severity of OCR during strabismus surgery.

In line with the findings in OCR severity, we also found that penehyclidine administration significantly attenuated the strabismus surgery-induced decrease of heart rate by 19.0% in the patient with OCR ($P<0.05$) (Fig. 5C).

**8. Penehyclidine shows no obvious negative effect on anesthesia recovery**

To investigate whether penehyclidine administration after anesthesia induction will impact anesthesia recovery, we analyzed the time to extubation, time stay in post-anesthesia care unit, use of antiemetics and analgesics, occurrence of severe dry mouth, facial flush, and drowsiness. As shown in Table 3, no significant difference was detected between penehyclidine and normal saline groups in all the indexes mentioned above. The findings suggest that penehyclidine did not delay anesthesia recovery or increase possible adverse effects.

|                                | Normal saline (n = 104) | Penehyclidine (n = 114) | $P$ value |
|--------------------------------|------------------------|-------------------------|----------|
| Post-operative antiemetic      | 4 (3.9%)               | 1 (0.9%)                | 0.195    |
| Post-operative analgesia       | 1 (1%)                 | 3 (2.7%)                | 0.623    |
| Time to extubation (min)       | 25 (16)                | 25(13)                  | 0.922    |
| PACU stay time (min)           | 59 (30)                | 60 (30)                 | 0.732    |
| Severe dry mouth               | 0                      | 0                       | -        |
| Facial flushing                | 1 (1%)                 | 1 (0.9%)                | 1.000    |
| Drowsiness                     | 0                      | 1 (0.9%)                | 1.000    |

Occurrence of post-operative antiemetic or analgesic requirement, severe dry mouth, facial flushing and drowsiness are expressed as numbers and percentages (%) of patients, and compared by Fisher’s exact test between normal saline group and penehyclidine group. Time to extubation and PACU stay time are expressed as medium (IQR) and compared by Mann-Whitney U test between normal saline group and penehyclidine group. PACU, post-anesthesia care unit.

**Discussion**
The significant finding in this study is that administration with penehyclidine after anesthesia induction significantly attenuated incidence and severity of both postoperative oculocardiac reflex and postoperative nausea and vomiting in the patients with strabismus surgery. Penehyclidine should be considered as an effective intervention for the prevention of intraoperative oculocardiac reflex and postoperative nausea and vomiting in strabismus surgery.

PONV is a common complication after general anesthesia for surgery patients including those who undergoing strabismus surgery. The risk factors for the development of PONV include patient-related factors, anesthetic techniques, and type of surgery (17, 18). It is well known that female, non-smokers, PONV or motion sickness history, and the use of opioids are the most common risk factors(18). The inhalational anesthetics, ketamine, and etomidate increase the incidence of PONV, while the use of propofol, midazolam and free fluid infusion technique are believed to reduce its incidence(1, 19). Also, PONV risk is affected by different kinds of surgeries including strabismus surgery. For underaged patients, duration of surgery ≥ 30 min, age ≥ 3 years and receiving strabismus surgery are all independent risk factors of PONV (20, 21). Many drugs have been used for the prevention or treatment of PONV. The most widely used antiemetic drugs are 5-hydroxytryptamine (5-HT₃) receptor antagonists. The NK-1 receptor antagonists, corticosteroids, butyrophenone and antihistamines are also recommended. However, Each kind of antiemetic drugs raises different concerns just like the risk of QT prolongation in 5-HT₃ receptor antagonists and the effect on postoperative infection as well as blood glucose levels in corticosteroids (21, 22). Here in this study, we demonstrated that penehyclidine, an anticholinergic agent, significantly reduced PONV in strabismus surgery patients.

Consistent with previous reports that showing 38 ~ 68.2% PONV incidence in strabismus surgery, we found 54.8% of overall PONV incidence in normal saline group in this investigation. We also found that the patients showed a significant higher PONV incidence within 6 h after strabismus surgery. Notably, we demonstrated that administration of penehyclidine after anesthesia induction pronouncedly attenuated PONV incidence in patients with strabismus surgery. The severity of PONV was mitigated and the PONV incidence was significantly reduced in the underaged and adult male patients as well as in the adult female patients following penehyclidine administration.

Unexpectedly, we also found a significant effect of penehyclidine on the attenuation of oculocardiac reflex during strabismus surgery though that penehyclidine was previously considered as having no obvious effect on heart rate (12). Oculocardiac reflex is observed frequently in strabismus surgery with an incidence of 14 ~ 90% (4). Once stimulated by manipulation, the ophthalmic branch of the trigeminal nerve transports the sensory message to central nervous system, thereby causing impulses to exit the brainstem and transmit to the sinoatrial node and activate the vagal motor response, and ultimately leading to sinus bradycardia, atioventricular block, ventricular ectopy, ventricular fibrillation, hypotension, or even asystole (5). Thus, prevention and management of OCR is important. Several approaches have been applied to decrease the incidence of OCR. Immediately pausing surgery can suspend the reflex through removal of pressure to the eyeball or extraocular muscles; however, repeated pauses may disturb the process of surgery (5). Pretreatment with atropine or glycopyrrolate can attenuate the negative effect
of vagus nerve on heart rate during OCR through blocking peripheral type 2 muscarinic receptors of the heart; however, atropine or glycopyrrolate may result in undesirable dysrhythmia such as sinus tachycardia which may diminish cardiac output (5, 23). In this study, an overall OCR incidence of 77.9% was found in strabismus surgery patients while administration with penehyclidine significantly attenuated OCR. Penehyclidine reduced overall OCR incidence, and reduced the OCR severity as indicated by requirement for atropine to rescue. However, it is not clear whether the effect of penehyclidine on OCR is caused by its intrinsic type 2 muscarinic receptor block effect.

The main side effects of penehyclidine include dry mouth and central anticholinergic syndrome, similar to other anticholinergics (15). Moreover, its central sedative effect sometimes delays anesthesia recovery. In our investigation, 10 µg·kg−1 with an upper limit to 0.5 mg penehyclidine was used. The anesthesia recovery, as indicated by the time to extubation and the time staying post-anesthesia care unit, was not delayed in penehyclidine group compared to normal saline group. No patient complained of severe dry mouth and no patient developed central anticholinergic syndrome postoperatively. These may possibly be explained by limited maximal dose difference, and our patients undergoing minor surgery could drink free after surgery (24).

The anesthesia scheme design enhanced the strengths of this study. Agents including midazolam, etomidate, inhalational anesthetics or neostigmine were not used because potential effects on PONV. Besides, the randomization and double-blinded technique were strictly carried out during the investigation. As randomization was achieved by lottery method, patients allocated into the two groups were not equal. In subgroup analysis, the sample size of the subgroups also appeared imbalanced. In order to get more reliable outcomes, a stratified random sampling method is more suitable for pre-designed subgroup analysis.

Conclusions

In conclusion, this study identified penehyclidine, a widely preoperatively used anticholinergic drug in clinic, as an effective protector against intraoperative oculocardiac reflex and postoperative nausea and vomiting in the patients with strabismus surgery.

Abbreviations

OCR: oculocardiac reflex; PONV: postoperative nausea and vomiting; ECG: electrocardiograph; SpO2: saturation of pulse oxygen; bpm, beats per minute; IQR: interquartile range; 5-HT3: 5-hydroxytryptamine; NS: normal saline; EOM, extraocular muscles.

Declarations

Ethics approval and consent to participate
This study was prospectively approved by the Human Research Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (#2019-SR-238) and a written informed consent was obtained from patients or their legal guardians.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the stipulations of ethics committee to protect individual privacy of patients but are available from the corresponding author on reasonable request.

Competing Interests

The authors declared that they have no competing interests.

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Authors’ Contributions

ZD contributed to study conception and design, and interpretation of data and drafted the article. JS, XC, TL and NL contributed to clinical investigation and data collection. JS and XM contributed to statistical analysis. All authors have read and approved the manuscript

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