Retrospective analysis of risk factors of postoperative nausea and vomiting in patients undergoing ambulatory strabismus surgery via general anaesthesia

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ABSTRACT

Background and Aims: Postoperative nausea and vomiting (PONV), one of the common complications following strabismus surgery, would delay the ambulatory discharge time. The aim of this retrospective study was to determine the risk factors of PONV in patients undergoing ambulatory strabismus surgery under general anaesthesia, with the treatments of dexamethasone and 5-HT₃ antagonist combination. Methods: We reviewed 721 consecutive patients (12–60 years old) undergoing ambulatory strabismus surgery under general anaesthesia at an academic eye centre between December 2016 and January 2019. Patients received prophylactic treatment of dexamethasone and 5-HT₃ antagonist combination during anaesthesia induction, and PONV was evaluated during the early recovery period before discharge. Results: The dexamethasone and 5-HT₃ antagonist combination effectively reduced the incidence of PONV (3.05%, 22/721), and the patients who experienced PONV had statistically prolonged phase II recovery time as compared those who did not (P = 0.006). The sum of the extraocular muscles manipulated and the use of nalbuphine (vs flurbiprofen axetil) were the independent risk factors for PONV (P < 0.05). Conclusion: The sum of the extraocular muscles manipulated and the use of nalbuphine are potentially modifiable risk factors for PONV after strabismus surgery with the treatments of dexamethasone and 5-HT₃ antagonist combination.

Key words: Anaesthesia, ophthalmic, postoperative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) after strabismus surgery remains a common complication with an incidence as high as 30–49%. Rather, strabismus surgery itself has been identified as an independent risk factor for PONV. It should be noted that PONV following strabismus surgery could increase the patient’s discomfort, delay the discharge and eventually increase medical costs.

Although strabismus surgery can be conducted under local anaesthesia combined with sedation, strabismus surgery is more painful than other types of ophthalmic surgery like cataract surgery and blepharoplasty, and an inadequate level of sedation may result in increased risk of globe perforation due to involuntary head movement. Instead, the surgery is routinely performed under general anaesthesia at our centre because general anaesthesia can provide adequate analgesia and sedation with the development of short-acting anaesthetics and the use of laryngeal mask airway (LMA) to ensure adequate ventilation.
Rather than types of extraocular muscles manipulated,\(^9\) anaesthetic techniques such as opioids and inhalational agents are suggested to increase the incidence of PONV in adults, although the precise aetiology of PONV following strabismus surgery remains to be elucidated. Further, duration of anaesthesia (>30 min) and age (>3 years) also play important roles in the development of PONV.\(^{[3]}\) Unfortunately, whether such risk factors including anaesthetic techniques and type of analgesics also contribute to PONV following strabismus surgery remains unknown in adolescents and adults under general anaesthesia.

Dexamethasone and 5-HT\(_3\) antagonist combination has been recommended for the prevention of PONV in vulnerable patients.\(^{[8]}\) In this study, we retrospectively analysed the risk factors of PONV following strabismus surgery under general anaesthesia with the treatment of dexamethasone and 5-HT\(_3\) antagonist combination.

**METHODS**

The cases of 721 consecutive patients who underwent ambulatory strabismus surgery between February 2016 and January 2019 at Zhongshan Ophthalmic Center were retrospectively reviewed. Zhongshan Ophthalmic Center is the largest eye institute in China. The study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (Ref. 2017KYPJ118) and registered at http://www.chictr.org.cn (No. ChiCTR1800014831). Only patients aged between 12 to 60 years, who underwent general anaesthesia for the ambulatory surgery were enrolled in the present retrospective analysis. We excluded the in-hospital patients because of severe complications during the surgery or from anaesthesia or no family members accompanied for home readiness; we also excluded the patients whose medical records were incomplete.

Anaesthesia was induced with propofol 2.5 mg/kg and fentanyl 1-2 μg/kg, and muscle relaxants (cisatracurium, 0.1–0.2 mg/kg). Anaesthesia was maintained by total intravenous anaesthesia (TIVA) (propofol and remifentanil) or inhalational anaesthesia (sevoflurane or desflurane) ventilated by LMA. Ventilation was controlled with 8–10 mL/kg tidal volume to keep end-tidal CO\(_2\) level at 35–45 mmHg. Nonsteroidal anti-inflammatory drugs (NSAID) such as flurbiprofen axetil (1 mg/kg IV, Tide, Beijing, China) or nalbuphine (0.1 mg/kg) were used to prevent postoperative pain. Dexamethasone (5 mg for adults or 0.1 mg/kg for children), combined with 5-HT\(_3\) antagonist (palonosetron [0.25 mg for adults or 0.005 mg/kg for children] or tropisetron [0.1 mg/kg]) were routinely intravenously administrated at induction of anaesthesia to prevent PONV.

After the surgery and treatments with neostigmine (0.02 mg/kg, IV) and atropine (0.01 mg/kg, IV) to antagonise muscle relaxants, the LMA was removed when sufficient recovery of spontaneous ventilation was confirmed. The patients were then transferred to the post-anaesthesia care unit (PACU) for further care (phase I recovery). All patients, who met the Aldrete score of ≥9, were then transferred to the phase II recovery room with an accompanying family member. The patients were considered ready for discharge when their post-anaesthesia discharge scoring system scores (PADSS) were at least 9 (early recovery).\(^{[9]}\) Patients were permitted to drink water as soon as requested after the PADSS of at least 9 was met. All patients were telephoned by a nurse to ask about emergency events and unanticipated hospitalisation within 24 h after the surgery (late recovery). Postoperative adverse events were recorded during the early and late recovery periods.

The primary outcomes were incidences of PONV during the early recovery period. The PONV was defined by the presence in symptoms of nausea, and retching, vomiting or both regardless of episodes.\(^{[10]}\) Anaesthesia time, surgery time, anaesthetic techniques, the use of opioids or NSAIDs, awakening time, time to Aldrete score ≥9, time to PADSS ≥9 in phase II recovery were analysed as a possible risk factor for PONV.

Continuous variables are presented as median (interquartile range [IQR]) and compared with the Mann-Whitney U test. Frequency variables were expressed as numbers (proportion) and analysed by the Chi-squared test or Fisher’s exact test. Propensity score matching (PSM) and binary multi-factor logistic regression (LR) analysis (forward LR method) were used for multivariate analysis to determine risk factors for PONV. Considering that longer phase II recovery time is a result instead of a reason for the occurrence of PONV, the phase II recovery time was excluded in the multi-factor analysis. Further, the surgery time was excluded in the multi-factor analysis because it is highly correlated with the sum of the extraocular muscles manipulated. PSM was conducted for the other...
seven positive factors except for the sum of extraocular muscles manipulated because of its non-duality. Data were analysed using IBM SPSS Statistics 24 with PSMATCHING 3.04 (IBM, New York, US) and R-3.2.0 (R Core Team). A P value < 0.05 was considered statistically significant.

RESULTS

A total of 721 patients (361 males and 360 females) were included in the final retrospective analysis. 266 patients (36.89%) underwent left strabismus surgery, 249 patients (34.54%) underwent right strabismus surgery and 206 patients (28.57%) underwent bilateral strabismus surgery [Table 1]. 163 patients received one-muscle surgery, 428 patients received two-muscle surgery, 110 patients received three-muscle surgery, 19 patients received four-muscle surgery while one patient received the five-muscle procedure, and the average surgery duration was 27.00 min [Table 1]. As shown in Table 1, 615 patients received TIVA whereas 106 patients (14.70%) received inhalational anaesthesia. PONV occurred in 22 patients with the incidence of 3.05% [Table 1]. The patients were then divided into two groups: PONV-absent group (n = 699) and PONV-present group (n = 22). There were no significant differences in height, weight, physical status, phase I recovery time, LMA size, use of dexmedetomidine and types of muscle correction between the two groups [P > 0.05, Table 2].

The use of tropisetron, nalbuphine and midazolam were more frequent in the PONV-present group than in the PONV-absent group [P < 0.05, Table 2]. Younger age and longer phase II recovery time were found in the PONV-present group than those in the PONV-absent group [all P < 0.05, Table 2]. Surgical manipulation of the inferior rectus muscle, superior rectus muscle and lateral rectus muscle presented no significant differences between the two groups [P > 0.05, Table 2]. However, there was a trend of increased patients in the PONV-present group underwent superior rectus muscle correction than those did in the PONV-absent group [P = 0.052, Table 2]. Furthermore, the sum of extraocular muscles manipulated in the PONV-present group was greater than the PONV-absent group [P = 0.001, Table 2].

Distributions of propensity score between the two groups were similar, and standardised differences were concentrated on ‘0’ after matching [all P values > 0.05, Table 3 and Supplemental Figure 1a-e], in PSM analysis results, there were no significant differences in gender, use of midazolam, use of tropisetron (vs palonosetron) and superior rectus muscle correction [P > 0.05, Table 3], whereas the use of nalbuphine (vs flurbiprofen axetil) displayed significant differences between the two groups [P = 0.02, Table 3]. Finally, a binary multi-factor LR showed that the sum of extraocular muscles manipulated and the use of nalbuphine (vs flurbiprofen axetil) was identified as independent risk factors of the PONV [all P < 0.05, Table 4].

The area under the receiver operating characteristic (ROC) analysis showed that the curve for PONV in the model of risk factors was 0.76 [95% CI: 0.66–0.86, Figure 1]. The prediction formula for PONV was as follows:

Logit (P) = −5.00 + 0.89 × [the sum of surgical extraocular muscles] + 1.37 × 1 [if using nalbuphine (vs flurbiprofen axetil)]

DISCUSSION

In this retrospective analysis, we found that the incidence of PONV was 3.05% of 721 ambulatory strabismus surgical patients, indicating that PONV may no longer be a ‘big little problem’ in strabismus patients under general anaesthesia with the treatments of dexamethasone and 5-HT\textsubscript{3} antagonist combination.\[^1\] Moreover, we found that nalbuphine (vs flurbiprofen axetil) use and the sum of extraocular muscles manipulated were the risk factors for PONV following strabismus surgery.

[Figure 1: Receiver operating characteristic (ROC) curve for the model of risk factors: female; sum of surgical extraocular muscles; nalbuphine (vs flurbiprofen axetil). P <0.001, AUC = 0.80 (95% CI: 0.73–0.87), Logit (P) = −5.00 + 0.89 × [sum of surgical extraocular muscles] + 1.37 × 1 [if using nalbuphine (vs flurbiprofen axetil)]]
It's been reported that the prevalence of strabismus is 1.93%, and surgical management of strabismus is one of the treatments to correct sensorial adaptation disorders. Unfortunately, patients often complained about the unpleasant experience of PONV after strabismus surgery. Severe PONV would result in a range of complications, including wound dehiscence and pulmonary aspiration. Further, because PONV is one of the main items in the PADSS, by which the ambulatory patients can be guided to discharge home, sustained PONV would prolong discharge time. Indeed, we found that patients with PONV stayed longer in the phase II recovery room than those without PONV in the current study.

Many prophylactic antiemetic agents have been recommended to minimise this postoperative side effect, a combination of dexamethasone and 5-HT3 receptor antagonist has been suggested to prevent PONV in patients with a high risk. The previous studies revealed that a combination of dexamethasone and ondansetron is more effective than ondansetron alone in reducing PONV after strabismus surgery, our current regimen in preventing PONV includes a multimodality approach by using a combination of dexamethasone and 5-HT3 receptor antagonist during anaesthesia induction. We found that the incidence of PONV following strabismus surgery with the combination of dexamethasone and 5-HT3 receptor antagonist is significantly lower than that reported in previous studies, this can be explained by the anaesthetic agents selected and non-use of N2O in our study.

All patients underwent surgery under general anaesthesia in the present study, it has been demonstrated that anaesthetic technique would affect the incidence of PONV, the notion is supported...
Table 2: Single-factor analysis results

| PONV, No. (%)                  | Absent, 699 (96.95%) | Present, 22 (3.05%) | P     |
|--------------------------------|----------------------|---------------------|-------|
| Age (y)*, median (IQR)         | 24.00 (19.00-31.00)  | 20.50 (16.50-24.75) | 0.04  |
| Height (cm)*, median (IQR)     | 164.00 (158.00-170.00) | 160.50 (157.75-170.75) | 0.53  |
| Weight (kg)*, median (IQR)     | 55.00 (49.00-65.00)  | 55.50 (44.75-66.00)  | 0.43  |
| Duration of surgery (min)*, median (IQR) | 26.00 (20.00-35.00)  | 33.00 (19.50-41.50)  | 0.15  |
| Recovery period I (min)*, median (IQR) | 30.00 (22.00-40.00)  | 26.00 (20.00-37.25)  | 0.37  |
| Recovery period II (min)*, median (IQR) | 35.00 (20.00-60.00)  | 56.00 (29.50-95.50)  | 0.006 |
| LMA size*, No. (%)             | 4.00 (4.00-4.00)     | 4.00 (4.00-4.00)     | 0.35  |
| 2, No. (%)                     | 4 (0.57%)            | 0 (0%)               |       |
| 2.5, No. (%)                   | 2 (0.29%)            | 0 (0%)               |       |
| 3, No. (%)                     | 80 (11.44%)          | 2 (9.09%)            |       |
| 4, No. (%)                     | 488 (69.81%)         | 19 (86.36%)          |       |
| 5, No. (%)                     | 125 (17.88%)         | 1 (4.55%)            |       |
| Gender*, No. (%)               |                      |                     | 0.09  |
| Female                         | 345 (49.36%)         | 15 (68.18%)          |       |
| Male                           | 354 (50.64%)         | 7 (31.82%)           |       |
| ASA-grade*, median (IQR)       | 1.00 (1.00-1.00)     | 1.00 (1.00-1.00)     | 0.51  |
| Ⅰ, No. (%)                     | 631 (90.27%)         | 21 (95.45%)          |       |
| Ⅱ, No. (%)                     | 68 (9.73%)           | 1 (4.55%)            |       |
| Surgical eye*, No. (%)         |                      |                     | 0.86  |
| Left                           | 257 (36.77%)         | 9 (40.91%)           |       |
| Right                          | 241 (34.48%)         | 8 (36.36%)           |       |
| Bilateral                      | 201 (28.76%)         | 5 (22.73%)           |       |
| Intravenous or inhalational anaesthesia*, No. (%) | | | |
| Intravenous anaesthesia        | 594 (84.98%)         | 21 (95.45%)          | 0.23  |
| Inhalational anaesthesia       | 105 (15.02%)         | 1 (4.55%)            | >0.99 |
| Using sevoflurane              | 17 (16.19%)          | 0 (0%)               |       |
| Using desflurane               | 88 (83.81%)          | 1 (100%)             |       |
| Using dexametomidine*, No. (%) | 214 (30.62%)         | 7 (31.82%)           | >0.99 |
| Using dexamethasone*, No. (%)  | 699 (100%)           | 22 (100%)            |       |
| Using midazolam*, No. (%)      | 277 (39.63%)         | 14 (63.64%)          | 0.03  |
| 5-HT₃ antagonist*, No. (%)      |                      |                     |       |
| Using tropisetron              | 477 (68.24%)         | 21 (95.45%)          | 0.004 |
| Using palonosetron             | 222 (31.76%)         | 1 (4.55%)            |       |
| Analgesic*, No. (%)            |                      |                     |       |
| Using flurbiprofen axetil      | 463 (66.24%)         | 7 (31.82%)           | 0.002 |
| Using nalbuphine               | 236 (33.76%)         | 15 (68.18%)          |       |
| Surgical superior rectus muscle*, No. (%) | | | |
| Unilateral                     | 59 (4.39%)           | 5 (15%)              | 0.052 |
| Bilateral                      | 11 (0.82%)           | 0 (0%)               |       |
| Surgical inferior rectus muscle*, No. (%) | | | |
| Unilateral                     | 50 (3.72%)           | 2 (6%)               | 0.51  |
| Bilateral                      | 19 (1.41%)           | 2 (6%)               |       |
| Surgical superior oblique muscle*, No. (%) | | | |
| Unilateral                     | 63 (4.69%)           | 4 (12%)              | 0.39  |
| Bilateral                      | 22 (1.64%)           | 0 (0%)               |       |
| Surgical inferior oblique muscle*, No. (%) | | | |
| Unilateral                     | 130 (9.67%)          | 2 (6%)               | 0.63  |
| Bilateral                      | 44 (3.27%)           | 3 (9%)               |       |
| Surgical medial rectus muscle*, No. (%) | | | |
| Unilateral                     | 633 (47.10%)         | 24 (71%)             | 0.13  |
| Bilateral                      | 33 (2.46%)           | 0 (0%)               |       |
| Surgical lateral rectus muscle*, No. (%) | | | |
| Unilateral                     | 842 (62.65%)         | 15 (44%)             | 0.49  |
| Bilateral                      | 269 (20.02%)         | 11 (32%)             |       |
| Sum of surgical extraocular musclesa, Median (IQR) | 2.00 (2.00-2.00) | 2.00 (2.00-3.00) | 0.001 |
| 1, No. (%)                     | 161 (22.03%)         | 2 (9.09%)            |       |

Contd...
by that administration of propofol by TIVA has a prophylactic antiemetic effect. However, we did not find that the benefits of TIVA were greater in reducing the incidence of PONV than inhalational anaesthetic technique. We speculated that the antiemetic effects of combination of dexamethasone and 5-HT₃ receptor antagonist would cover up the influences of anaesthetic techniques;

[furthermore, remifentanil used in TIVA resulted in more consumption of the opioids, which may have induced PONV,][17] and there was a tendency of a high proportion of patients who received TIVA to display PONV in the present study [Table 2].

The type of surgical technique used for strabismus correction has been shown as one of the major factors in the incidence of PONV,[18] the previous study suggested that myopexy is associated with a significantly higher incidence of PONV than with the recess-resect technique.[19] In-line with the previous studies, we found that there is a tendency that the surgery on the superior rectus muscle is associated with the development of PONV [Table 2] because the traction of the muscle is tense and can easily induce ocular gastrointestinal reflex.[20] General anaesthesia can reduce the tension of muscle and facilitate the procedure to shorten the surgery time, which can reduce the incidence of ocular gastrointestinal reflex and may contribute to the low incidence of PONV. In the current study, we found that the average surgery time was 27 min, which is shorter than the surgeries conducted under local anaesthesia,[21] Accumulated evidence has suggested that duration of surgery >30 min was positively correlated with PONV,[3,22] which may explain the low incidence of PONV in the present analysis. Meanwhile, it’s thinkable that more extraocular muscles manipulated would lead to more traction time and longer surgery duration, our study demonstrated that the sum of extraocular muscles manipulated was one of the independent risk factors of PONV; while the finding cannot be supported by Joo et al.,[20] the small sample size may contribute to the difference.[20] Although there are many concerns that general anaesthesia would delay the discharge time for ambulatory strabismus surgery,[5] we found that

Table 2: Contd.,...

| PONV, No. (%) | Present, 22 (3.05%) | P |
|---------------|---------------------|---|
| 2, No. (%)    | 10 (45.45%)         |   |
| 3, No. (%)    | 7 (31.82%)          |   |
| 4, No. (%)    | 3 (13.64%)          |   |
| 5, No. (%)    | 0 (0%)              |   |

*By Mann-Whitney U test with two-side, †By Fisher’s exact test with two-sides, PONV=Postoperative nausea and vomiting; recovery period I: End of operation→Exit from PACU; recovery period II: Exit from PACU→PADS met 9; ASA=American Society of Anesthesiologists; LMA=Laryngeal mask airway; IQR=Interquartile range

Table 3: Propensity score matching results

| PONV          | Absent | Present | P   | OR (95% CI) | PSM Overall Balance Test (Hansen and Bowers) \( \chi^2 \) (P) |
|---------------|--------|---------|-----|-------------|-------------------------------------------------|
| Gender, No. (%) |        |         |     |             |                                                 |
| Male          | 316 (50.64%) | 7 (31.82%) | 0.13 | 2.20 (0.88, 5.47) | 2.61 (0.98) |
| Female        | 308 (49.36%) | 15 (68.18%) |     |             |                                                 |
| Using midazolam, No. (%) | 168 (49.12%) | 9 (75.00%) | 0.14 | 3.11 (0.83, 11.68) | 12.15 (0.15) |
| Using 5-HT₃ antagonist, No. (%) | 92 (50.27%) | 0 (0%) | >0.99 | 1.01 (0.99, 1.03) | 9.50 (0.39) |
| Using tropisetron | 91 (49.73%) | 1 (100%) |     |             |                                                 |
| Assistant analgesic, No. (%) |        |         |     |             |                                                 |
| Using flurbiprofen axetil | 160 (51.61%) | 3 (18.75%) | 0.02 | 4.62 (1.29, 16.54) | 9.44 (0.31) |
| Using nalbuphine | 150 (48.39%) | 13 (81.25%) |     |             |                                                 |
| Binary surgical superior rectus muscle, No. (%) | 40 (48.19%) | 4 (80%) | 0.36 | 4.30 (0.46, 40.12) | 3.44 (0.90) |

Table 4: Binary logistic regression of multi factors results

| PONV                             | \( \beta \) Coefficient | SE  | P    | EXP (\( \beta \)/OR (95% CI) | Omnibus Test \( \chi^2 \) (P) | Hosmer-Lemeshow Test \( \chi^2 \) (P) | Nagelkerke R² |
|----------------------------------|--------------------------|-----|------|-------------------------------|--------------------------------|--------------------------------------|--------------|
| Nalbuphine (versus flurbiprofen axetil) | 1.37                     | 0.47| 0.004| 3.93 (1.56, 9.87) | 23.52                          | 7.35 (0.50) | 0.13 |
| Age                              | -0.05                    | 0.03| 0.09 | 0.95 (0.90, 1.00) | (<0.001)                        |                                      |              |
| Sum of surgical extraocular muscles | 0.89                      | 0.27| 0.001| 2.44 (1.42, 4.21) |                                  |                                      |              |

All regression hypothesis tests are two-sided. PONV=Postoperative nausea and vomiting; IQR=Interquartile range
the discharge time in the present study was similar to that in patients under local anaesthesia, reported by the previous study,\(^2\) with the LMA and short-acting anaesthetics used.

Nalbuphine is indicated by the Food and Drug Administration (FDA) for moderate to severe pain,\(^2\) our previous study found that nalbuphine is an optimal analgesic to control postoperative pain after ophthalmic surgery.\(^2\) In the current study, we used either nalbuphine or NSAIDs to prevent the postoperative pain, and none of the patients declared severe pain or received an additional dose of analgesics during the phases I and II recovery periods. However, as a kappa-opioid receptor agonist and a partial mu-opioid receptor antagonist, nalbuphine has been reported to induce the same incidence of PONV as morphine.\(^2\) In this study, we found that patients with PONV displayed more frequent use of nalbuphine than those without PONV, and the use of nalbuphine (vs flurbiprofen axetil) was identified as a risk factor for PONV following strabismus surgery. The results indicated non-opioid analgesics should be the primary choice for postoperative pain management after strabismus surgery.\(^2\)

Although the benefits were achieved from the efforts to minimise the incidence of PONV, several limitations should be pointed out. First, this is a retrospective study, which may miss some important data because we did not evaluate the history of PONV. Second, most of the patients had a health status of the American Society of Anaesthesiologists (ASA) 1–2, which may result in the low incidence of PONV. Third, we did not analyse the incidence of PONV in the patients after discharging home, because PONV mostly occurs within the first 3 h after ambulatory surgery under general anaesthesia.\(^2\)

**CONCLUSION**

The sum of extraocular muscles manipulated and the use of nalbuphine (vs flurbiprofen axetil) are the independent risk factors in the development of PONV following ambulatory strabismus surgery under general anaesthesia with dexamethasone and 5-HT\(_3\) antagonist combination treatments.

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**Conflicts of interest**
There are no conflicts of interest.

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Supplemental Figure 1: (a) Effect of PSM for “Gender”. (b) Effect of PSM for “Using Midazolam”. (c) Effect of PSM for “Using Tropisetron or Palonosetron”. (d) Effect of PSM for “Using Flurbiprofen Axetil or Nalbuphine”. (e) Effect of PSM for “Binary Surgical Superior Rectus Muscle”