Desflurane anesthesia compared with total intravenous anesthesia on anesthesia-controlled operating room time in ambulatory surgery following strabotomy: a randomized controlled study

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Abstract
Background: Ophthalmic ambulatory surgery is preferred to be performed under general anesthesia either by total intravenous anesthesia (TIVA) or by inhalational anesthesia to increase the patient comfort. However, anesthesia-controlled time (ACT) can cause increased non-operative operating room (OR) time which may adversely affect the ORs efficiency. This study was aimed to compare the ACT of desflurane with that of propofol-remifentanil in strabismus ambulatory surgery.

Methods: From November 2016 to December 2017, a total of 200 strabismus patients (aged 18–60 years old, and scheduled for elective ambulatory surgery at Zhongshan Ophthalmic Center) were randomly assigned to receive either propofol-based TIVA (group TIVA) or desflurane anesthesia (group DES) for maintenance of anesthesia. The primary outcome was the extubation time. Secondary outcomes included surgical time, anesthetic time, OR exit time, and Phase I and II recovery time. The intraoperative incidences of hypotension, bradycardia and oculocardiac reflex (OCR), and the incidences of any post-operative complications were recorded. Mann-Whitney U test and Chi-square or Fisher exact tests were used to compare the two groups.

Results: We found that the extubation time (5.5 [3.9–7.0] vs. 9.7 [8.5–11.4] min, P < 0.001) and the incidence of prolonged time to extubation (0 vs. 6%, P = 0.029) in the DES group were significantly decreased compared with those in the TIVA group. The patients in the DES group displayed shorter OR exit time as compared with that in the TIVA group (7.3 [5.5–8.7] vs. 10.8 [9.3–12.3] min, P < 0.001). The patients using desflurane exhibited more stable hemodynamics during surgery than the patients using propofol-based TIVA, as demonstrated by lower incidences of hypotension (1% vs. 22%, P < 0.001), bradycardia (2% vs. 13%, P = 0.002), and OCR (17% vs. 44%, P < 0.001).

Conclusion: DES enhanced the anesthetic OR efficiency by reducing the extubation time and OR exit time, and provided more stable hemodynamics intra-operatively than TIVA in patients undergoing strabismus ambulatory surgery.

Trial registration: ClinicalTrials.gov, No. NCT02922660; https://clinicaltrials.gov/ct2/show/NCT02922660?draw=2&rank=1

Keywords: Desflurane; Propofol; Operating rooms; Efficiency; Strabismus; Ambulatory surgery

Introduction
The management of ophthalmic anesthesia is currently of particular interest to anesthetists because of its short length and fast-tracking characteristics.[1] Strabismus surgery has traditionally been conducted under regional anesthesia combined with monitored anesthesia care (MAC), but recently, general anesthesia has become favorable for ophthalmologists and patients for the following reasons: first, the airway can be secured while MAC may interrupt the succession of surgical procedures because of respiratory adverse events; second, general anesthesia can relax the tension of the extraocular muscle and immobilize the eyeball to facilitate the surgery; and third, general anesthesia can help reduce patient anxiety and increase patient satisfaction during the peri-operative period.[2,3]

There are more than 4000 strabismus surgical cases per year performed under general anesthesia at our eye center; hence, it is necessary to improve the operating room (OR) efficiency to satisfy the demands of the growing number of surgical cases.[4] Anesthesia-controlled time (ACT), which consists of anesthesia induction time, extubation time, and OR exit time, is one of the most important factors affecting
the OR efficiency. The ACT is typically dependent on the sequence of two consecutive surgical cases and thus adds to the complexity of OR scheduling. The interval between the end of surgery and extubation (extubation time) has drawn the attention of anesthetists because it can be affected by anesthetic regimens.

The anesthesia techniques commonly used for ophthalmic ambulatory surgery are total intravenous anesthesia (TIVA) and desflurane anesthesia (DES). A meta-analysis showed that desflurane reduced the time to extubation by 26% relative to propofol, whereas a retrospective study reported that TIVA was associated with faster emergence and a low incidence rate of prolonged time to extubation. Based on the limited evidence from retrospective analyses, it is still unclear which anesthesia technique is optimal for ophthalmic ambulatory surgery. This study was designed with the aim of comparing the ACT and incidences of complications between propofol-based TIVA and DES in patients undergoing strabismus ambulatory surgery.

Methods

Ethical approval

This prospective randomized controlled trial was approved by the Institutional Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University (No. 2016KYP038), and was registered before patient enrollment at ClinicalTrials.gov (No. NCT02922660). The study was conducted in accordance with the Declaration of Helsinki. The manuscript adheres to the CONSORT guidelines. Written informed consent was obtained from the enrolled patients.

Patient enrollment and study blinding

From November 2016 to December 2017, strabismus patients with American Society of Anesthesiologists (ASA) physical status class I–II, aged from 18 to 60 years, scheduled for short-duration ambulatory surgery (expected surgical duration <2 h) under general anesthesia were recruited for this study. Patients were excluded if they (1) had a body mass index >30 kg/m², (2) had a history of cardiopulmonary comorbidity, (3) had contraindications or previous adverse reactions to any of the drugs used, (4) abused drugs, (5) had chronic pain, (6) had a history of allergy to any of the study drugs, and (7) declined to sign the informed consent form.

All eligible patients were allocated to the study groups using a 1:1 simple randomized design. Subjects were randomly assigned into either the TIVA group (TIVA using propofol and remifentanil) or the DES group (inhalation anesthesia using desflurane) via a computer-generated table of random numbers. Each group equally contained 100 patients. Group assignments were then sealed in sequentially numbered opaque envelopes and were opened by the anesthetist once the patient gave written informed consent. The pre-operative assessments and group allocation were carried out by a trained research assistant who was not involved in anesthesia management and data processing. Only the anesthetist (who was responsible for anesthesia management) was privy to the patient assignments, and the patients, the research nurse (who was responsible for data collection) and the statistical staff (who was responsible for data analysis) were blinded to group identity.

Protocols of anesthe sia

The general anesthesia in both groups was all conducted by a senior attending anesthetist who was qualified and had 15 years of work experience. No pre-medication was given. Upon arrival in the OR, all patients were routinely monitored by non-invasive blood pressure (NIBP) measurements, electrocardiogram (lead II), heart rate (HR), pulse oxygen saturation level (SpO₂), end-tidal carbon dioxide partial pressure (PETCO₂), and bispectral index (BIS). The induction of anesthesia was conducted with propofol 2 mg/kg and fentanyl 1 μg/kg. Laryngeal mask airway (LMA, Tuoren Company, Xinxing, China) insertion was facilitated with cisatracurium 0.1 mg/kg. Before surgical incision, flurbiprofen axetil 100 mg, dexamethasone 5 mg and palonosetron 250 μg were respectively administered to prevent for post-operative pain, nausea, and vomiting, respectively.

In the TIVA group, anesthesia was maintained using target-controlled infusion (TCI) with propofol (AstraZeneca, London, UK) at an effect-site concentration (Ce) of 2.0 to 4.0 μg/mL and remifentanil 0.15 μg·kg⁻¹·min⁻¹ in 100% oxygen at a flow rate of 2 L/min. In the DES group, the desflurane (Baxter, Deerfield, USA) vaporizer was maintained within 6 to 8 vol% under a flow rate of 2 L/min with 100% oxygen in a closed breathing system. The Ce for TCI with propofol and the inhaled desflurane concentration were adjusted upward and downward by 0.2 to 0.5 μg/mL and 0.5% to 2.0 vol%, respectively, when necessary based on a BIS value between 45 and 55 and the hemodynamic changes. The patients were ventilated with a tidal volume of 6 to 8 mL/kg, and the ventilatory frequency was adjusted to maintain a PETCO₂ concentration between 35 and 40 mmHg.

If any sign of insufficient anesthesia appeared such as body movement, lacrimation, tachycardia or hypertension (ie, HR or NIBP increased beyond more than 20% of their levels before anesthesia), and spontaneous respiration was recovered during the maintenance period, the following methods were adopted: the Ce for TCI with propofol or the inhaled desflurane concentration was adjusted upward by 0.2 to 0.5 μg/mL or 0.5 to 2.0 vol%, respectively. If these were insufficient, cisatracurium 0.05 mg/kg or fentanyl 0.5 μg/kg was also administered. After stabilization was achieved, the doses of anesthetics were returned to maintenance levels.

We defined oculocardiac reflex (OCR) as a sudden reduction in HR of more than 20% from the baseline during extraocular muscle movement (EOM) according to a previous study. Treatment of the OCR was followed by stopping the traction for the EOM. Hypotension was defined as a systolic blood pressure <90 mmHg, and a HR that dropped below 50 beats/min was recorded as bradycardia. If
severe hypotension occurred intra-operatively, and fluid replacement as well as reduction of anesthetic agents were insufficient, then epinephrine 5 to 10 mg was intravenously administered; or if a HR less than 50 beats/min developed (including the HR during OCR not returning to baseline), atropine 0.5 mg was intravenously injected for rescue.

Upon completion of the surgery and application of the surgical dressing, all anesthetic agents were discontinued. Neostigmine 1.0 mg and atropine 0.5 mg were intravenously used to reverse the residual neuromuscular blocking. The lungs were ventilated with a fresh gas flow of 100% oxygen at 6 L/min. Then, the LMA was removed when patients responded to verbal commands, and regained adequate spontaneous respiration (ie, tidal volume reached at least 3 to 4 mL/kg with the $P_{15}CO_2$ less than 45 mmHg). We defined prolonged time to extubation as when the time interval from application of the surgical dressing to extubation was ≥15 min.12 If the patient developed coughing, breath holding, or desaturation to an $SpO_2$ of <90% during or immediately after LMA removal, 100% oxygen via a face mask was applied with a ventilation assistant. When adequate respiration and hemodynamic stability were confirmed, patients were transferred to the post-anesthesia care unit (PACU) for continuous monitoring to further evaluate the recovery.

**Post-operative recovery and follow-up**

All patients were continuously assessed for Phase I recovery using the modified Aldrete score in the Phase I recovery unit of the PACU.13 Patients who had a modified Aldrete score ≥9 were then transferred to the Phase II recovery unit with an accompanying family member. Patients were considered ready to discharge when the post-anesthesia discharge scoring system (PADSS) score was 9 or more.14 Post-operative pain was measured by a numerical rating scale (NRS, 0–10, 0 being no pain, 1–3 mild pain, 4–6 moderate pain, and 7 or more treated as severe pain), and flurbiprofen axetil 50 mg was given as a rescue analgesic if the NRS score exceeded 4. Severe and persistent post-operative nausea and vomiting (PONV) was treated with tropisetron 5 mg, if necessary. Any in-hospital complications happened in PACU were recorded. All patients were followed up by telephone 24 h after discharge home to inquire whether they experienced unanticipated hospitalization for any emergency medical events. Post-discharge complications, for example, post-discharge nausea and vomiting (PDNV), post-operative pain (moderate and severe), dizziness, pharyngalgia, and fever, were also recorded. Meanwhile, all patients were interviewed for intra-operative awareness using a modified Brice interview.13 A standardized follow-up template for our institution was used to prevent patients not understanding during the calls. All data in our study were collected by a research nurse blinded to the study groups.

**Outcome measures**

The primary outcome was the extubation time (time from application of the surgical dressing to extubation). Secondary outcomes included surgical time (time from incision to surgical completion and dressings applied), anesthetic time (time from anesthesia induction to extubation), OR exit time (time from completion of surgery to departure from the OR), Phase I recovery time (time from arrival in the Phase I recovery unit until the modified Aldrete score achieved at least 9), and Phase II recovery time (time from arrival in the Phase II recovery unit until the PADSS score achieved at least 9). The intra-operative incidences of hypotension, bradycardia, and OCR were evaluated. Post-operative complications occurred in the PACU, and post-discharge complications, as well as unanticipated hospitalizations occurring 24 h after discharge, were also recorded.

**Sample size calculation**

The sample size was estimated based on our pilot study of the extubation time in strabismus patients using DES (7.23 ± 1.52 min, $n = 10$) with those using TIVA (8.06 ± 1.82 min, $n = 10$). Thus, each group will be recommended to have a minimum sample size of 90, with a power to 90% and a two-tailed $\alpha$ level of 5%. Considering the 10% drop-out rate, 100 participants will be required for each group with the total sample size of 200.

**Statistical analysis**

Intention-to-treat analysis was used in this study. The normality of the data was checked by the Kolmogrov-Smirnov test. Continuous data with a normal distribution are expressed as mean ± standard deviation, while data with a skewed distribution are expressed as the median (interquartile range). Categorical data are expressed as the number of patients (percentage). Analyses of the surgical time, anesthetic time, extubation time, OR exit time, and Phase I and II recovery times were performed with the Mann-Whitney U test. Chi-square or Fisher exact tests were used, as appropriate, for categorical variable comparisons between groups, including the incidences of hypotension, bradycardia, and OCR during the surgery, and post-operative complications. A two-tailed $P$ value less than 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

**Results**

A total of 200 patients who met the inclusion criteria were initially enrolled and equally assigned to either the DES group or the TIVA group in this trial. One patient in the DES group and two patients in the TIVA group were lost to follow-up after discharge from the hospital. A CONSORT flow diagram displaying the number of participants who were randomly allocated, who were excluded, who received intended intervention, and who were analyzed is described in Figure 1. The patient demographic data are presented in Table 1.

The timeframes of the procedure and subsequent recovery durations showed that there was no significant difference between the two groups with regard to the surgical time ($P = 0.313$), anesthetic time ($P = 0.651$), Phase I recovery
time \((P = 0.831)\) or Phase II recovery time \((P = 0.573)\) [Table 2]. The extubation time \((9.7 \pm 11.4)\) vs. \(5.5 \pm 3.9\) min, \(P < 0.001\) and OR exit time \((10.8 \pm 12.3)\) vs. \(7.3 \pm 5.5\) min, \(P < 0.001\) in the TIVA group were significantly longer than that in the DES group [Table 2].

Six percent of patients displayed prolonged time to extubation in the TIVA group, which was more than that in the DES group \((P = 0.029)\) [Table 3]. During the anesthetic procedure, the incidences of hypotension and bradycardia, as well as OCR, were significantly lower in the DES group than in the TIVA group \((1\% vs. 22\%, P < 0.001, 2\% vs. 13\%, P = 0.002\) and \(17\% vs. 44\%, P < 0.001\), respectively) [Figure 2]. It should be noted that three patients using inhaled desflurane had severe cough during the extubation period [Table 3]. The incidence rates of PONV and post-operative moderate-to-severe pain (NRS score \(\geq 4\)) in the Phase II recovery unit...
were similar between both groups (all P = 1.000) [Table 3].

A total of 197 subjects were successfully followed up the day after the surgery (a drop-out rate of 1.5%). No significant differences in post-discharge complications, including PDNV (P = 0.279), post-operative moderate-to-severe pain (NRS score ≥4 (P = 0.977), dizziness (P = 0.553), pharyngalgia (P = 0.692), and fever (P = 0.497) were found between the DES group and the TIVA group [Table 3]. No patient complained of anesthesia awareness at the 24-h post-operative follow-up. Additionally, none of the patients in either group experienced unanticipated hospitalization after discharge home.

**Discussion**

In the present study, we observed that inhalational anesthesia using desflurane reduced the extubation time by 43% (a median difference of 4.2 min) and OR exit time by 32% (a median difference of 3.5 min), and provided more stable hemodynamics intra-operatively compared to propofol-based TIVA in patients undergoing strabismus ambulatory surgery. Moreover, the post-operative complications were comparable for the two anesthesia techniques.

Considering the short length of the procedure in strabismus surgery, the ACT might be relatively long compared with the surgical duration, inviting critical evaluation of interventions to reduce the ACT. Previous studies indicated that ACT, including the time to exit from the OR after extubation and the total OR stay time, might be affected by extubation time. However, extubation time usually differs among types of anesthetic regimens. The results in the present study have shown that desflurane reduced the median extubation time relative to propofol-fentanyl by 43% and the median time to OR exit by 32%, demonstrating that desflurane is more likely to fast-track the recovery of strabismus patients and potentially reduce the ACT following ambulatory surgery. The reductions in ACT would reasonably contribute to optimal scheduling of the OR workflow by ophthalmic surgery. Dexter and Epstein previously reported that each 1 min reduction in OR time results in an overall 1.0- to 1.2-min reduction in regularly scheduled labor costs, as a result, such small reductions in ACT, achieved by decreasing in extubation time and OR exit time, as reported in our study, can be treated as having considerable economic benefits.

Additionally, prolonged time to extubation is an important factor influencing OR efficiency by increasing the ACT. Prolonged extubation times make surgeons and nursing staff wait longer for the next surgery. Several lines of evidence have demonstrated that longer-than-average ACTs could strongly affect OR efficiency by increasing OR staffing costs and decreasing hourly productivity. In our study, patients under propofol-based TIVA experienced a higher incidence rate of prolonged time to extubation compared with the surgical duration, indicating critical evaluation of interventions to reduce the ACT.
with those under DES (no patient displayed a prolonged time to extubation). The variances of these two anesthesia techniques can be explained by the accumulation of propofol after continuous infusion during the surgery, and the potential for the fast “washout” of desflurane (which has the lowest blood-gas partition coefficient of the available halogenated agents) after discontinuation.

Our result is consistent with the results of several published studies in other types of surgery.\[6\]

The hemodynamics investigated in our study were more stable in patients maintained with desflurane, who displayed lower incidences of hypotension and bradycardia as well as OCR, compared to those maintained with propofol-based TIVA. These results can be explained by the potent sympatholytic and synergistic suppressive effects of intra-operatively administered propofol and remifentanil, respectively, on the sympathetic nervous system.\[12\] In addition, no patient complained of anesthetic awareness after the surgery. In other words, intra-operative desflurane maintenance without opioids (remifentanil) can achieve adequate anesthetic potency for strabismus surgery, and its vagolytic activity contributes to stable hemodynamics.\[23,24\] The OCR is a parasympathetic response during EOM traction, which leads to decreases in both HR and contractility of the heart.\[25\] Severe OCR would interrupt the procedure and prolong the surgical time. Previous studies reported that OCR can be affected by anesthetics, anesthesia depth, and surgeon experience.\[11,26,27\] In agreement with the study of Choi et al.\[26\] we found that DES reduced the incidence of OCR by 27% compared with propofol-based TIVA.

Although the post-operative complications (including in-hospital complications after the surgery and post-discharge complications 24 h after discharge home) were comparable for the two anesthesia techniques, we should note that three patients in the DES group displayed severe cough during extubation. Severe cough may lead to increased intraocular pressure, suture damage, surgical site bleeding, and even detrimental hemodynamic changes.\[28\] These phenomena can be regarded as a fast recovery of the airway reflex caused by desflurane.\[23\] Wu et al.\[29\] indicated that turning off the anesthetic drugs later can prevent coughing and straining during emergence, but might result in delayed recovery. Reyes et al.\[24\] suggested that smooth extubation without coughing in patients receiving DES may be feasible at a minimum alveolar concentration of 0.62 during extubation preparation, and further study is needed to focus on this adverse event. Otherwise, the incidences of nausea and vomiting, as well as post-operative pain (NRS score ≥4), were slightly increased after discharge home in both groups. These phenomena indicate that additional doses of antiemetics and analgesics should be prescribed for patients after the surgery.\[30\]

There were some limitations in this study. First, we only involved patients with ASA physical status class I to II, and the results may not be applicable to other patients who have severe health problems, as these would be cofounding factors affecting perioperative hemodynamics and the metabolism of anesthetics. Second, although the data collector and analyzer were blinded, the anesthesia provider was not blinded, which may lead to bias considering the proficiency of anesthetists. Despite these limitations, our results take advantage of the unique aspects of strabismus surgery and are useful for the management of ophthalmic anesthesia.

In conclusion, although desflurane inhalational anesthesia or propofol-based TIVA are both suitable for ophthalmic surgery, our study demonstrates that desflurane retains the fast-tracking recovery properties of reduced extubation time and OR exit time with stable hemodynamics, which may efficiently and economically enhance the OR workflow, especially for the short-length procedures such as strabismus ambulatory surgery.

**Availability of data and materials**

The data used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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**Conflicts of interest**

None.

**References**

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