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Comparison of the Time to Orientation between Combining Propofol with Sevoflurane or Sevoflurane in Patients Undergoing Endoscopic Trans-Nasal Surgery: A Randomized Controlled Trial

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Abstract

Background: This study investigates whether combining propofol and sevoflurane for anesthesia maintenance results in faster emergence compared to sevoflurane alone in patients undergoing endoscopic trans-nasal surgery. **Methods:** Thirty-eight patients were randomized to receive either sevoflurane alone (Group S, n = 19) or propofol plus sevoflurane (Group PS, n = 19) targeting a BIS range of 40 - 60. The primary outcome was time to orientation. Secondary outcomes included time to spontaneous ventilation, eye-opening to sound, extubation, hemodynamics, agitation, coughing, analgesic needs, and PONV. **Results:** The median time to orientation was significantly longer in Group PS (12 minutes, IQR 6-16) compared to Group S (6 minutes, IQR 5-12) ($P < 0.05$). Subgroup analysis of cases exceeding 120 minutes of anesthesia showed significantly longer orientation times in Group PS (14.07 ± 6.20 minutes) versus Group S (8.5 ± 3.92 minutes) ($P < 0.05$). Extubation time was also longer in Group PS (8.63 ± 4.67 minutes) versus Group S (5.95 ± 2.91 minutes) ($P < 0.05$). Heart rates were higher overall in Group PS ($P < 0.05$). **Conclusion:** Using BIS-targeted anesthesia, combining propofol with sevoflurane resulted in a longer time to orientation than sevoflurane alone in patients undergoing endoscopic trans-nasal surgery, particularly when anesthesia exceeded 120 minutes.

Keywords

Propofol, Sevoflurane, Trans-Sphenoidal Surgery, Endoscopic Sinus Surgery, Functional Endoscopic Sinus Surgery (FESS)

1. Introduction

Endoscopic trans-nasal surgeries, such as trans-sphenoidal pituitary surgery and endoscopic sinus surgery for nasal polyposis, chronic sinusitis (functional endoscopic sinus surgery; FESS), tumor excision and treatment of sinus mucocele, are now common surgical procedures. Both have similar anesthetic goals, including the provision of a clear surgical field, immobilization for surgical precision, the maintenance of hemodynamic stability, and a smooth and rapid emergence from anesthesia [1]-[4].

While anesthetic goals for trans-sphenoidal pituitary surgery include smooth and rapid emergence to facilitate prompt neurologic assessment [3] [4], gentle awakening in nasal surgery is also important because coughing and straining during emergence frequently produce undesirable incidences of post-surgical bleeding [1]. Moreover, early recovery of consciousness is also essential to prevent post-operative airway complications, which may occur due to nasal packing or intra-operative opioid use [3]. The options are broad with respect to the acceptable anesthetics for endoscopic trans-nasal surgeries, and the various agents can be used for the induction and maintenance of anesthesia [4]. Conventional general anesthesia is performed by induction with an intravenous anesthetic agent (such as propofol) and maintenance with a volatile anesthetic (such as sevoflurane), as well as with opioids and muscle relaxants [5].

Recently, the combination of propofol and sevoflurane for maintenance has been suggested due to the beneficial effects of each agent [5]. Total intravenous anesthesia (TIVA) with propofol decreases the incidence of post-operative nausea and vomiting (PONV) and decreases cerebral blood flow and intracranial pressure, as well as attenuates post-operative pain [5] [6]. In addition, it was found that patients, who had received propofol for maintenance, had exhibited better post-operative cognition scores [3] [7]. In FESS, reports indicated that TIVA with propofol reduces intra-operative bleeding, thus improving visualization of the surgical field compared to inhalation anesthesia [8]. Moreover, sevoflurane has cardioprotective effects and coronary vasodilatory effects [5] [6]. Liang *et al.* reported that the co-administration of sevoflurane and propofol had resulted in faster awakening and extubation than sevoflurane alone had. This was most likely possibly due to the lower administered amounts of each anesthetic drug, which results in relatively faster drug elimination [5] [9]. Another study performed by Uchinami *et al.* revealed that the time to extubation had been faster with the sevoflurane/propofol combination than with propofol alone, but the difference was not determined to be significant [10]. Moreover, the combination of sevoflu-

rane and propofol showed a lower incidence of emergence, coughing, and agitation than sevoflurane had for maintenance [5]. Furthermore, Feng *et al.* reported that the application of propofol combined with sevoflurane could increase respiration and circulation stability in patients, who had undergone radical gastrectomies [9].

Additionally, the incidence of post-operative nausea and vomiting (PONV) after neurosurgery is relatively higher than that after other general surgeries [11] [12], and the consequences of PONV during neurosurgery are devastating. These include increased intracranial pressure, leading to intracranial hemorrhage and brain herniation [13]. Moreover, in trans-sphenoidal pituitary surgery, another complication that may occur after repeated intense Valsalva maneuvers (*i.e.*, coughing or vomiting) is the re-opening of a CSF leak, which worsens the risk of subsequent meningitis [14]. Therefore, even though the overall incidence of PONV after trans-sphenoidal surgery was lower than that, which had been reported in most studies of neurosurgical patients [15], the use of PONV prophylaxis, including propofol for anesthesia, would be considered beneficial for patients. For FESS, the incidence of PONV has not been well reported. However the presence of blood in the stomach, intra-operative opioid use, and inflammation of the uvula and throat may be contributing factors. Also, PONV prophylaxis should also be applied [8].

Since the effects of the co-administration of propofol and sevoflurane on recovery profiles in patients undergoing endoscopic trans-nasal surgery have not been investigated, we hypothesized that for maintenance, the combination of propofol and sevoflurane may result in a faster and smoother emergence than sevoflurane alone in patients undergoing endoscopic trans-nasal surgery.

2. Methods

2.1. Study Design

Thirty-eight patients (18 - 60 years of age), with an ASA physical status of I-III and a BMI of 18 kg/m^2 - 35 kg/m^2, who underwent elective endoscopic trans-nasal surgery from 2021-2022 at the Faculty of Medicine's Srinagarind Hospital at Khon Kaen University, were enrolled. The exclusion criteria were emergency surgeries, as well as patients with unstable hemodynamics, end-stage renal disease, end-stage cirrhosis, cognitive impairment, a history of uncontrolled hypertension, heart blocks that were greater than first degree, obstructive sleep apnea, chronic use of pain control, allergies to the drugs that were used in the study, and pregnant patients. Patients for whom extubation could not be achieved due to any conditions, such as aspiration, unstable hemodynamics or surgical complications and who had received reintubation in the PACU for any reason were excluded. Patients were randomly allocated into two groups via a computer-generated random list with permuted block randomization with allocation concealment via opaque sealed envelopes.

2.2. Anesthesia Protocol

After informed consent was obtained, all eligible patients were NPO after midnight, and no pre-operative sedatives or analgesics were administered. Standard monitoring methods, including electrocardiograms, non-invasive blood pressure measurements, pulse oximeters, and body temperature probes, were used. The bispectral index (BIS) was monitored before induction with a BIS™ (Covidien) in accordance with the manufacturer's instructions. Pre-medications, including fentanyl 1 mcg/kg - 2 mcg/kg IV and dexamethasone 8 mg IV [16], were given before the induction of anesthesia. General anesthesia was then induced with 1.5 mg/kg - 2.5 mg/kg IV propofol, followed by 0.1 mg/kg - 0.2 mg/kg IV cisatracurium for intubation. After the induction drugs had been given but before tracheal intubation, continuous invasive blood pressure was measured from the radial artery.

During the maintenance phase, cisatracurium (1 mg/mL) at 1 - 2 mcg/kg/min and fentanyl (10 mcg/mL) at 1 mcg/kg/h were infused. The sevoflurane group **(Group S)** received titratable sevoflurane, and the combination of sevoflurane and propofol group **(Group PS)** received sevoflurane fixed at 0.5 MAC and a titratable propofol infusion. The anesthetic drugs, which were used, were adjusted to achieve a BIS of 40 - 60 for both groups. Anesthesia was maintained by controlled positive pressure ventilation with an air-oxygen mixture to maintain $EtCO_2$ at 30 mmHg - 35 mmHg. In addition, a body temperature equal to or greater than 35 degrees Celsius was achieved by a forced air warming device and warmed intravenous fluid. The MAP was maintained within 20% of baseline with the use of vasopressors and vasodilators.

The hemodynamic variables (HR and MAP) and the BIS, which were recorded during surgery, were as follows: [3]

1) Before and after intubation (pre-intubation and post-intubation—maximal rise within 3 min. of tracheal intubation).

2) Before and after nasal packing of saline swabs soaked in adrenaline (pre-nasal packing and post-nasal packing—maximal rise within 3 min).

3) Infiltration of the nasal mucosa with a local anesthetic solution of lidocaine and adrenaline (pre-infiltration and post-infiltration—maximal rise within 3 min).

4) Insertion of Hardy's self-retaining nasal speculum (pre-speculum and post-speculum—maximal rise within 3 min).

5) At the time of incision (maximal rise).

At the end of surgery, 8 mg of ondansetron IV was administered [17]. The cisatracurium infusion was discontinued when the operation seemed to be nearly finished (approximately 30 minutes before finishing). Other anesthetic drugs, such as propofol, fentanyl, and sevoflurane, were discontinued when 4 twitch responses (TOF of 4 counts) appeared. Neuromuscular blockade was then reversed with 0.05 mg/kg neostigmine IV and 0.02 mg/kg atropine IV. One hundred percent oxygen was provided at a flow rate of 6 L/min. Extubation was achieved when the TOF ≥ 0.9, the BIS ≥ 85, spontaneous breathing with a tidal volume > 5 mL/kg, and an intact gag reflex were reached. The patient was able to follow commands, such as

opening his or her eyes, clenching his or her fists, and sustaining a head lift for 5 seconds.

The times from anesthetic drug discontinuation to spontaneous ventilation, opening the eyes in response to sound, extubation, and orientation (by correctly answering the question, *"What is your name?"*) were evaluated at 30 second intervals by an assessor, who had been blinded to the type of maintenance anesthesia. The time to orientation after the patients were extubated was represented as t0 and was then evaluated at 30 second intervals for 20 minutes until the patients could answer the question correctly. The incidence of sustained and repetitive cough movements with a head lift and the incidence of agitation were recorded based on the Ricker sedation-agitation scale. Any score on the sedation-agitation scale ≥ 5 was defined as an emergence agitation.

At the post-anesthetic care unit (PACU), the pain score and need for analgesics were recorded via a numerical rating scale (NRS) by an assessor, who had been blinded to the anesthetic regimen. If the NRS score was ≥ 4, fentanyl 1 mcg/kg IV was given to the patients. Fentanyl was given every 10 minutes after the last dose if the NRS score was still ≥ 4. The incidence of nausea and vomiting was evaluated (0 = no nausea; 1 = mild nausea; 2 = severe nausea requiring antiemetics; and 3 = retching, vomiting or both) at 2 hours after surgery. If the nausea and vomiting score was ≥ 2, metoclopramide 10 mg IV was given. Complications, such as a massive loss of blood, hypotension, hypertension, awareness, and reintubation which had occurred in the PACU, were also recorded and managed according to standard guidelines.

2.3. Sample Size

Since there had been no previous data regarding the time to orientation in the sevoflurane combined with propofol group and sevoflurane alone group, the sample size calculation was based on the time to orientation between the sevoflurane group and the propofol group. Choi *et al.* reported that the time to orientation of sevoflurane is 10.0 ± 3.9 minutes, whereas that of propofol is 14.2 ± 5.7 minutes [18]. We calculated the sample size in order to compare two independent means by using the standard deviation of the control group (sevoflurane group), which was 3.9 minutes. Regarding the minimal clinically important difference (MCID), Choi *et al.* [18] and Liang *et al.* [5] reported the time to extubation between the sevoflurane/propofol group and the sevoflurane group at 8.0 ± 1.8 min. vs. 12.8 ± 1.6 min. Therefore, it was decided to use an MCID of 4 minutes. With a precision of 20% and confidence level of 95%, the calculated sample size was 15 patients per group. Based on an anticipated dropout rate of 10%, the overall sample size was determined to be 38 patients.

2.4. Statistical Analyses

The statistical analyses were accomplished via STATA10.1 (College Station, TX, USA). For the normally distributed continuous data, the independent t test was

used, and the data was presented as means and SDs. In contrast, if the data was not normally distributed, the Mann-Whitney U test was used, and the results were presented as medians and interquartile ranges. For the dichotomous variables, logistic regression was used to study the relationships between the variables and the outcomes, and the results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, peri-operative hemodynamics, which are repeated-measures variables, were analyzed via the generalized estimating equation (GEE), which was followed by the Bonferroni correction so that the differences in outcomes could be studied. $P < 0.05$ was considered to be statistically significant.

3. Results

Thirty-eight patients completed the study. Both groups were comparable with respect to the demographic data (Table 1).

Table 1. Demographic data.

Demographic data	Group S (n = 19)	Group PS (n = 19)
Gender		
Male	8 (42.11)	11 (57.89)
Female	11 (57.89)	8 (42.11)
Age (years)	45.84 ± 10.93	43.11 ± 10.60
ASA physical status		
ASA I	5 (26.32)	4 (21.05)
ASA II	13 (68.42)	14 (73.68)
ASA III	1 (5.26)	1 (5.26)
Weight (kg)	65 (60 - 70)	64 (54 - 80)
Height (cm)	164.53 ± 13.45	163.16 ± 9.59
BMI (kg/m²)	25.17 ± 3.39	24.61 ± 4.40
History of motion sickness/PONV	1 (5.26)	1 (5.26)
Current smoker	1 (5.26)	1 (5.26)
Duration of surgery (min)	79 (60 - 128)	110 (60 - 137)
Duration of anesthesia (min)	125 (110 - 180)	160 (109 - 190)
Intraoperative fentanyl used (mcg)	209.95 ± 100.23	220.45 ± 92.31
Intraoperative cisatracurium used (mg)	17 (13 - 25)	17 (12.4 - 22)
Total blood loss (mL)	200 (30 - 600)	200 (100 - 450)

Note: Data are presented as a number (%), mean (SD).

The median time to orientation in the PS Group was longer than that of the S Group. The median time in the PS Group was 12 minutes (IQR 6-16 minutes), whereas the median time in the S Group was 6 minutes (IQR 5-12 minutes) ($P < 0.05$) (Figure 1). Subgroup analysis revealed that for operations with an anesthesia

time > 120 minutes, the mean time to orientation had been 14.07 ± 6.20 minutes for the PS Group and 8.5 ± 3.92 minutes for the S Group ($P < 0.05$). By contrast, in operations with an anesthesia time ≤ 120 minutes, the time to orientation between the two groups was comparable (Figure 2). The mean times to extubation in the PS Group and the S Group were 8.63 ± 4.67 minutes and 5.95 ± 2.91 minutes, respectively ($P < 0.05$) (Table 2). Overall, the PS Group had exhibited higher heart rates than the S Group had ($P < 0.05$) (Table 3).

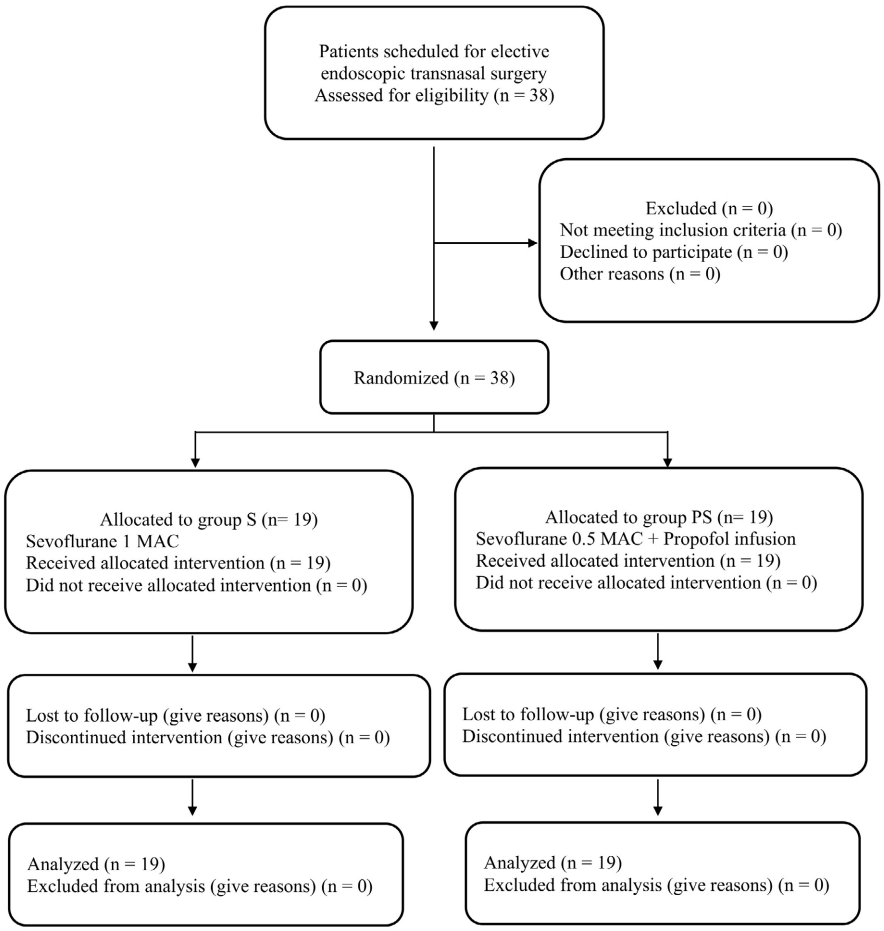

Figure 1. Consort flow diagram.

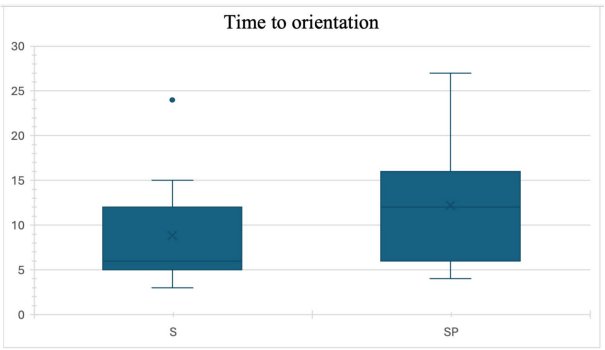

Figure 2. Time to orientation.

Table 2. Recovery profiles.

	Group S (n = 19)	Group PS (n = 19)	MD (95% CI)	Sig.
Time to orientation (min)	6 (5 - 12)	12 (6 - 16)	−3 (−7,0)	0.045*
Anesthesia time ≤ 120 min	9.22 ± 6.78	7 ± 3	2.22 (−4.83, 9.27)	0.505
Anesthesia time > 120 min	8.5 ± 3.92	14.07 ± 6.20	−5.57 (−10.19, −0.95)	0.020*
Time to spontaneous ventilation (min)	3 (1 - 5)	3 (2 - 4)	0 (−1, 1)	0.847
Time to eye opening (min)	4 (3 - 8)	8 (4 - 10)	−2 (−5, 0)	0.077
Time to extubation (min)	5.95 ± 2.91	8.63 ± 4.67	−2.68 (−5.25, −0.12)	0.041*
	Group S (n = 19)	**Group PS (n = 19)**	**OR (95% CI)**	**Sig.**
Incidence of serious coughing (N%)	6 (31.58)	9 (47.37)	1.95 (0.53, 7.1)	0.319
Incidence of emergence agitation (Ricker sedation-agitation scale ≥ 5) [5] (N%)	5 (26.32)	5 (26.32)	1 (0.25, 4.02)	>0.999

Note: *Statistically significant; Data are presented as a number (%), mean (SD).

Table 3. Perioperative hemodynamics.

	Difference (95%CI) = group PS − group S	Sig.
Overall MAP (mmHg)	2.26 (−10.62, 15.15)	0.731
Overall HR (bpm)	11 (0.7, 21.3)	0.036*

Note: *Statistically significant.

The time to spontaneous ventilation and the time to the opening of the eyes in response to sound were similar in both groups. The incidence of serious coughing and agitation during emergence, the need for analgesics in the PACU, the incidence of PONV, and the intra-operative blood pressure levels were comparable between the groups.

4. Discussion

Since studies have demonstrated that sevoflurane and propofol have additive effects due to their separate binding sites and converging pathways of action on the $GABA_A$ receptors [5] [19] [20], more researchers have focused on the co-administration of sevoflurane and propofol to obtain the benefits of these two drugs. According to Liang *et al.*, their study was performed in elective gastrointestinal surgery under combined general/epidural anesthesia. The patients were allocated randomly to sevoflurane (Group S) or the sevoflurane/propofol regimen (Group PS). During maintenance, the BIS values were maintained at between 40 - 60, which was the same as this study. However, Group PS was maintained with titratable sevoflurane and propofol fixed at a 1.2 mcg/mL target plasma concentration, which was equivalent to 0.52% sevoflurane or approximately 0.3 MAC (the Ce_{50} ratio of sevoflurane to propofol equaled 0.43 vol%/mL/mcg) [5], whereas our study used sevoflurane 0.5 MAC and titratable propofol, which should be equiva-

lent to 0.5 MAC when we assume that BIS 40 - 60 can usually be achieved by using 1 MAC. Therefore, our study used more propofol than their study had. Moreover, according to Jellish *et al.*, the recovery time from anesthesia, including extubation and command response, was significantly shorter in the sevoflurane group than in the propofol group in surgical procedures that had lasted up to three hours [21]. Most likely, this is the reason why our results contradicted theirs. Moreover, subgroup analysis was performed to study the effects of prolonged infusions of propofol. It was found that in operations with anesthesia times > 120 minutes, the time to orientation in the PS Group had been significantly greater than that of the S group, whereas in operations with an anesthesia time ≤ 120 minutes, the time to orientation was comparable between the two groups.

Regarding the peri-operative hemodynamics, we observed a significant increase in HR and blood pressure during intubation. The cardiovascular responses, including increased HR and blood pressure due to intubation, were lower in the PS Group, possibly due to the vasodilatation and negative inotropic effects of propofol [3]. However, the overall HR in the PS Group was significantly greater than that of the S group, which is probably due to the higher baseline HR in the PS Group. However, there were no differences in the use of vasopressors or vasodilators between the two groups.

There were several limitations to this study. Firstly, the effects of only one combination of propofol and sevoflurane were studied. Other methods of combinations were not evaluated in this study, and further investigation may be needed to find the optimal combination. Secondly, our study was a single center trial study consisting of 38 patients, who had only undergone endoscopic trans-nasal surgery. Thus, its generalizability is still limited. Thirdly, since the sample size calculation was based on the time to orientation, the sample size may not be adequately sufficient to assess other recovery profiles, such as the incidence of agitation and coughing, the need for analgesics in the PACU, and the incidence of PONV.

5. Conclusion

A longer time to orientation than sevoflurane alone had. This was especially true when the anesthesia time had exceeded 120 minutes.

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Trial Registration

This study was reviewed and approved by the TCTR (Thai Clinical Trials Registry) committee (TCTR20210924006).

Research Quality and Ethics Statement

This study was approved by the Human Research Ethics Committee of Khon Kaen

University as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE641356). Furthermore, all eligible patients signed informed consent before entry into the study.

Availability of the Data and Materials

The data and materials are available from the corresponding author upon reasonable request.

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Prior Presentation

Part of this study was previously presented as an oral presentation at the Asian Australasian Congress of Anesthesiologists (AACA) 2022 in conjunction with the 99th Annual Meeting of The Korean Society of Anesthesiologists (KSA) and the 74th Annual Meeting for The Korean Pain Society (KPS). The oral presentation was presented under the title: *Comparison of the Time to Orientation between Combining Propofol with Sevoflurane or Sevoflurane in Patients Undergoing Endoscopic Trans-nasal Surgery*: *A Randomized Controlled Trial*.

Conflicts of Interest

The authors had no competing interests.

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