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ORIGINAL RESEARCH ANESTHESIOLOGY

Comparison of recovery time with target controlled infusion of propofol with sevoflurane anesthesia using bispectral index monitoring in vitrectomy surgery

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Abstract

Background: Rapid recovery after anesthesia is critical and is associated with the anesthetic agents used. The bispectral index (BIS) monitoring to guide anesthetic agents' doses may play a significant role in the recovery time. This study compared recovery time after Target Controlled Infusion (TCI) of propofol with sevoflurane anesthesia by using BIS monitoring during vitrectomy surgery.

Methodology: This was a prospective observational, randomized study on 40 patients aged 18–65 y, physical status ASA I–II, body mass index (BMI) 18–30 kg/m^2, who underwent vitrectomy surgery. Subjects were randomly assigned into two groups, Group P – the TCI propofol group, and Group S – the sevoflurane group. Subjects in the Group P received TCI propofol (Schnider), and subjects in the Group S received sevoflurane for anesthesia maintenance, with a targeted BIS score of 40–60. Inj. fentanyl 1 µg/kg was administered if there was an increase in blood pressure, heart rate and/or BIS that could not be overcome by increasing the dose of TCI propofol or sevoflurane. Recovery time was calculated from when the maintenance regimen was stopped until the patient was able to obey simple commands. Recovery time, fentanyl consumption, postoperative agitation, nausea and vomiting incidence were noted and analyzed with SPSS v21.0 for Windows. T–Test or Mann–Whitney U test was performed to analyze the data.

Result: Recovery time in the Group P [11.5 (5–25) min)] was not significantly different from the Group S [9 (4–18) min, p = 0.139]. Total fentanyl consumption was higher in the Group P than in the Group S (1.765 vs. 1.428 µg/kg). The frequency of agitation during recovery was higher in the Group S than in the Group P (30% vs. 20%)

Conclusion: There was no significant difference in recovery time between TCI propofol and sevoflurane anesthesia using BIS monitoring in vitrectomy. Total fentanyl consumption was higher in the propofol group than in the sevoflurane group. The impact of these anesthetic regimens on postoperative agitation needs further investigation.

Key words: Intravenous anesthesia; Bispectral index monitoring; BIS; Propofol; Sevoflurane; Target Controlled Infusion; TCI; Vitrectomy

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1. Introduction

Quick recovery is a much desired aspect of anesthesia. Prolonged recovery time from general anesthesia may be associated with severe complications, such as hypoxemia, hypoventilation, hypercarbia, and upper respiratory tract obstruction etc.[1] Recovery time depends on the anesthetic agents used, patients' comorbidities, and the surgical factors (duration and type of the

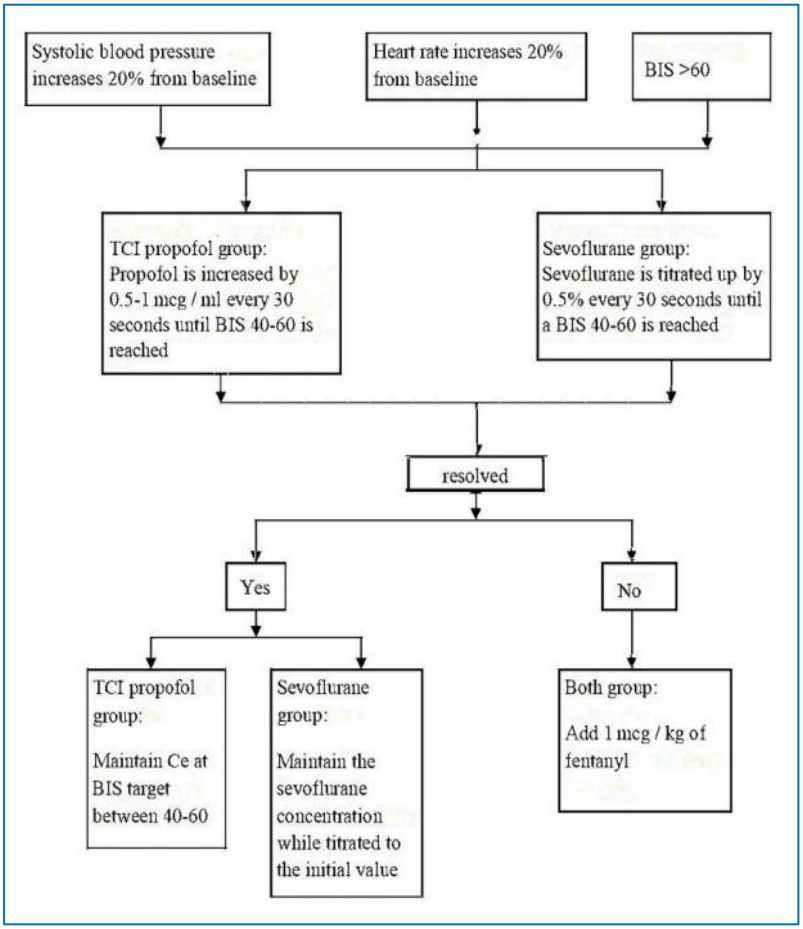

Figure 1: TCI propofol and sevoflurane dose adjustment and fentanyl addition algorithm

surgery).[2] Bispectral Index (BIS) monitoring is a monitor that has been used to measure the depth of the hypnotic component of anesthesia. Adjusting the dose of anesthetics according to BIS values had been known to be associated with faster recovery.[3]

Vitrectomy is a relatively short procedure that aims to decrease retinal traction by cleaning blood, debris, and the vitreous humor tissue to offer better access to the retina.[4] The anesthetic technique required in vitrectomy is different from other surgeries in that it should provide good hemodynamic stability and a short recovery time.[5] Sevoflurane is an inhalational anesthetic agent that can be easily administered, rapidly titrated, and has a wide margin of safety.[6] Propofol is an alternative short–acting intravenous anesthetics that can be given with targeted controlled infusion (TCI), which allows delivery of a precise drug concentration in a specific organ or body compartment.[7] Selection of appropriate anesthetic agent, between TCI propofol and sevoflurane, with BIS monitoring in vitrectomy, can shorten recovery times and operating room turnout time.

We compared the recovery time between TCI propofol and BIS controlled sevoflurane anesthesia in vitrectomy surgery, and also the difference in postoperative agitation, nausea and vomiting, during recovery between the two treatment regimens.

2. Methodology

This study was a prospective observational, randomized study. The independent variables in this study were TCI propofol and sevoflurane, and dependent variables were recovery time, post operative agitation, nausea and vomiting during recovery. This research was registered in www.clinicaltrials.gov (NCT04865991). After ethical approval from the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (879/UN2.F1/ETIK/2017) and informed consent, patients aged 18–65 y, body mass index 18 – 30 kg/m2, American Society of Anesthesiologists (ASA) status I–II, who were scheduled for vitrectomy surgery under general anesthesia, at Kirana's Eye Operating Theatre Cipto Mangunkusumo National General Hospital, were recruited in this study. Patients with hemodynamic instability, allergy, raised intracranial pressure, and history of malignant hyperthermia were excluded. Before surgery, patients with hearing disturbance, history of alcohol, opioids or psychotropic drug consumption, suffering from a neuropsychiatric disease, and electrolyte imbalance were also excluded from this study. Patients who experienced intraoperative cardiorespiratory disturbance, surgery lasting less than 35 min, and patients with temperature abnormalities before being extubated from LMA would be excluded from the trial.

2.1. Sample size

The sample size in this trial was calculated by using an unpaired numerical analytic equation as seen below.

$$n1 = n2 = 2\left(\frac{(Z\alpha + Z\beta)S}{x1 - x2}\right)^2$$

n1 = the sample size on group 1

n2 = the sample size on group 2

Zα = conventional multiplier for alpha = 0.05 (1.96)

Zβ = conventional multiplier for power = 1.28

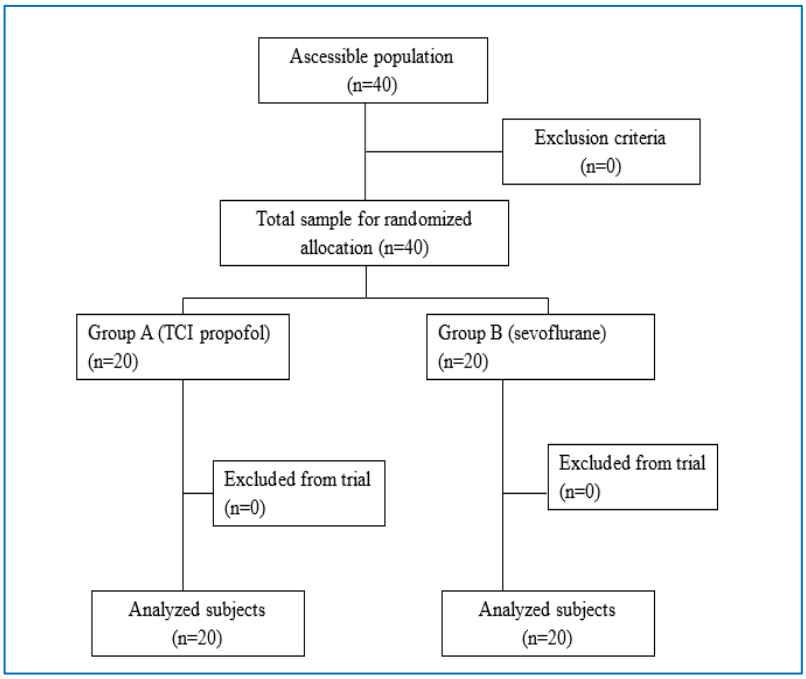

Figure 2: CONSORT study flow diagram

X1–X2 = the difference the investigator wishes to detect

S = population variance

The difference that investigators wished to detect was 2 points (x1–x2), population variance (S) was assumed 1.846, conventional multiplier for alpha 0.05 was 1.96 and conventional multiplier for power was 1.28. Therefore, the equation worked as below:

$$n1 = n2 = 2\left(\frac{(1.96 + 1.28)1.846}{2}\right)^2$$

$$n1 = n2 = 17.88\ (\sim 18\ \text{subjects})$$

The sample size that was calculated from the equations was 18 subjects. Ten percent of total subjects were added for drop–out possibility; thus, 20 subjects were recruited for each group with a total sample size of 40 subjects.

All subjects were recruited with a consecutive sampling method and randomly assigned into two groups, the Group P, and Group S. Block random allocation was done for all subjects by using the random allocator program Winpepi.

2.2. Study Protocols

Peripheral venous catheters were placed in all subjects. Subjects in the Group P had one specific intravenous catheter for propofol infusion apart from medication or intravenous fluid line. In comparison, subjects in the Group S were cannulated only with one venous catheter. Midazolam 0.05 mg/kg and fentanyl 1 µg/kg were given as premedication. Subjects in the TCI Propofol group received TCI propofol (Schneider) with targeted Ce 4–5 µg/ml for anesthesia induction and maintenance. Subjects in the Group S received intravenous propofol 1–2 mg/kg. Bispectral index (BIS) scores in both groups were titrated down to 50. Laryngeal mask airway (No. 3 or

4) was inserted three min after atracurium 0.25 mg/kg was administered. All subjects were ventilated with tidal volume 8 ml/kg, @12 times/min and FiO2 50%.

Subjects in the Group P received TCI propofol for anesthesia maintenance; Ce value was titrated until a targeted BIS score of 40–60 was achieved. Subjects in the Group S received sevoflurane 2 volume%, which were titrated up/down every 5 min to get a targeted BIS score of 40–60. Blood pressure, heart rate, oxygen saturation, and BIS scores were monitored every 5 min. Fentanyl 1 µg/kg was added if there was an increase in blood pressure, heart rate and or BIS score that could not be overcome by increasing the dose of TCI propofol or sevoflurane. The TCI propofol and sevoflurane dose adjustment and fentanyl addition algorithm can be seen in Figure 1.

Surgery was considered complete when the palpebral retractor had been removed. After spontaneous ventilation reverted, neostigmine 0.04 mg/kg and atropine 0.04 mg/kg were given for reversal. The laryngeal mask was removed when the anesthesia was still deep enough, and subjects were monitored afterward. The time to discontinue TCI propofol and sevoflurane was recorded (T0). When the patient was fully awake and could follow simple commands, such as raising hands was recorded (Tp). Recovery time was the duration from T0 to Tp. Unwanted events during recovery, such as agitation (unpleasant state of extreme arousal) and nausea–vomiting (unpleasant sensation often accompanied by the urge to vomit, and vomiting is the forceful expulsion of gastric contents through the mouth) were recorded. Total fentanyl usage during surgery was also recorded. Statistical analysis was performed using SPSS v. 21.0 software for Windows. T–Test or Mann–Whitney U test were done depending on the data normality test.

3. Results

Forty subjects were enrolled and randomized; all completed the interventions and follow–up. Results were reported according to Consolidated Standards of

Table 1. Subjects' characteristics

Characteristics	Group P n = 20	Group S n = 20
Age (y)	42.80 (± 11.29)**	47.35 (± 12.47)**
BMI (kg/m^2)	25.13 (± 9.95)**	25.29 (± 3.84)**
ASA physical status, n (%)		
ASA 1	7 (35.0)**	4 (20.0)**
ASA 2	13 (65.0)**	16 (80.0)**
Gender, n (%)		
Male	15 (75.0)**	11 (55.0)**
Female	5 (25.0)**	9 (45.0)**
Surgery duration (min)	55 (35–155)*	55 (35–155)*
Intraoperative blood pressure		
Systolic (mmHg)	115.35 (12.942)**	112.85 (18.731)**
Diastolic (mmHg)	76.3 (10.22)**	71.85 (14.342)**
BIS Score		
After induction	41.65 (10.85)**	34.45 (7.46)**
Intraoperative	34.74 (6.4)**	44.89 (7.6)**
End of Anesthesia	41.35(12.39)**	48.1 (8.55)**
$EtCO_2$ (mmHg)	32.1 (3.422)**	35.05 (3.59)**
Ce TCI propofol (µg/mL)	3.475 (1.03)**	
Sevoflurane concentration used (vol%)		2.1(0.35)**

**Median (min–max); **Mean (SD)*

Reporting Trials (CONSORT) guidelines (Figure 2). Baseline and perioperative variables were comparable between the two groups (Table 1).

During anesthesia, the Ce values of the propofol TCI group were successfully maintained below 50. Ce value was started in high value, decreased in mid–anesthesia, and slightly increased at the end of anesthesia. The sevoflurane concentration did not increase or decrease more than 1 volume% throughout the anesthesia. Total intraoperative fentanyl consumption in the Group P was higher than in the Group S e.g., 1.765 µg/kg vs. 1.428 µg/kg respectively (Table 2).

Median recovery time in the Group P was 11.5 (5 – 25) min, while in the Group S was 9 (4 – 18) min. There was no significant difference in recovery time between the TCI propofol and sevoflurane groups (p = 0.139). The incidence of postoperative agitation was higher in the Group S compared to the Group P. There was no postoperative nausea and vomitus incidence found in both groups (Table 2).

The intraoperative BIS value was lower in the Group P compared to the Group S. However, in both groups, there was no significant fluctuation in the BIS value (Figure 3A). Ce TCI value of propofol was high at the start of anesthesia and decreased mid–operation and increased towards the end of anesthesia. However, the Ce value towards the end of anesthesia was lower than the beginning of anesthesia (Figure 3B). The sevoflurane concentration increased intraoperatively adjusted according to the BIS value. The increase in intraoperative sevoflurane concentration did not exceed 1 vol% (Figure 3C).

4. Discussion

Anesthetic agents' recovery times are closely related to their pharmacokinetics and pharmacodynamics.[4] Age, gender, body mass index (BMI), and ASA physical status affect the pharmacokinetics as well as the pharmacodynamics of the anesthetic agents. In this study, age, body mass index (BMI), and ASA physical status were comparable in both groups.

The mean age in propofol group subjects was 42.8 y, and 47.35 y in the Group S. Geriatric patients were not included due to their higher sensitivity to anesthesia agents. In pediatric patients, who often have prolonged recovery due to hypothermia and reduced metabolism activity, were excluded from this trial. Patients with high BMI need larger doses than patients with normal BMI to get the same plasma concentration due to their extensive distribution volume. BMI subjects in both treatment arms were comparable (25.59 kg/m^2 in the Group P and 25.29 in the Group S, Table 1).[8] There were more males in the Group P than in the Group S. Males have more extensive fat distribution and tend to have a longer recovery time than females.[8]

4.1. Recovery time

We titrated sevoflurane and propofol dose according to the BIS score, ensuring both arms had the same level of anesthesia. The use of BIS can ensure optimum anesthesia, which might lead to a shorter recovery time.[9] BIS score is also a better predictor of patient response than patient's cardiovascular status. [9]

Table 2: Recovery time, agitation, mean of total fentanyl dose

Variable	Group P n = 20	Group S n = 20	p–value
Recovery time (median, range)	11.5 (5–25)	9 (4–18)	0.139 [a]
Agitation, n (%)	16 (80.0)	14 (70.0)	
Mean of total fentanyl dose (μg) (mean ± SD)	113 ± 41.49	96.75 ± 38.19	
Mean of total fentanyl used (μg/kg)	1.765	1.428	

[a]Mann–Whitney U test; significant p–value < 0.05

The median recovery time of the Group P was 11.5 (5–25) min. The median recovery time from the Group S was 9 (4–18) min. These results were more prolonged than the previous study, which had been performed in laparoscopic surgery and might be due to the residual effect of midazolam and fentanyl given. [9] Midazolam and fentanyl might still have their sedation effect at the end of surgery since the median duration of surgery in this study were 55 (35–155) min (Table 1).

Sevoflurane concentration was stable throughout the surgery. The early phase of surgery would need more significant sevoflurane consumption, reflecting the early phase of uptake of volatile anesthetics when a high concentration gradient existed between alveolar and exogenous gas supply. After 2 hours, the hourly consumption would become relatively constant, denoted that an equilibrium state had been attained. [9] In this study, due to the type of surgery, which provoke less pain than other types of surgery, combined with BIS monitoring, the fluctuation of sevoflurane concentration was less than 1 volume% throughout the surgery.

4.2. Sevoflurane and TCI propofol recovery time

Sevoflurane group has a shorter recovery time than the Group P but was not statistically significant (p = 0.139, Table 2). Previous studies performed in a different types of surgery or which had utilized different tools to estimate anesthetic consumption, had different results compared with our study.[10–13] As previously explained, the residual effect of midazolam and fentanyl used during induction might affect the recovery profile.

Fentanyl was given intermittently as needed during anesthesia in this study. Total fentanyl dose was higher in the Group P (Table 2). Propofol does not diminish nociceptive pain. However, sevoflurane does have analgesic properties mediated by GABAergic signaling, although its molecular mechanism has not been clearly understood.[14] Thus, additional analgesics were needed in the Group P. The same result had earlier been found in in a study in gynecologic surgery.[15] Fentanyl might extend propofol duration of action and affect the central nervous system. Further research needs to be done with a longer surgical duration and by using an ultra–short–acting opioid so that the residual effect of midazolam and fentanyl would not exist at the end of anesthesia.

Higher agitation rate was found in the Group S. There were 4 (20%) incidents of agitation in the Group P during the recovery period and 6 (30%) in the Group S. This finding is consistent with another study that compared agitation incidence between sevoflurane and propofol in adult patients.[3] Propofol, as an anesthetic agent, was related to smooth recovery, euphoric effect, and residual sedative effect in the early stages of emergence. Propofol also has a lower incidence of postoperative nausea and vomiting and hangover, associated with a lower incidence of postoperative emergence agitation. Another theory that suggested the cause of postoperative emergence delirium is the fast recovery time of anesthetic agent, increasing the sensitivity to stimulation from the environment, triggering a functional dissociation state.[3]

5. Limitations

There were several limitations in the present study. First, the end–tidal concentration of inhalational anesthesia agents was not measured. The inhaled anesthetics end–tidal concentration is the most representative measurement for the alveolar concentration. This current study provides an impetus for further research examining the effects of various anesthetic agents on recovery time in vitrectomy and other short procedures. Second, the effects of TCI and BIS focused on infusion dose adjustment rather than loading dose. Therefore, evaluation on long–term surgeries versus short–term surgeries should be conducted in the future.

6. Conclusion

There was no significant difference in recovery time between TCI propofol anesthesia and sevoflurane anesthesia, when monitored with bispectral index in vitrectomy. Total fentanyl consumption was higher in the TCI propofol group than in the sevoflurane group. The impact of these anesthetic regimens on postoperative agitation needs further investigation.

7. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

8. Author Contributions

Study concept and design: AT, RBS and LSA; analysis and interpretation of data: AT and RBS; drafting of the manuscript: LSA; critical revision of the manuscript for important intellectual content: AT, RBS and LSA; statistical analysis: LSA

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