Prospective evaluation of remifentanil-propofol mixture for total intravenous anesthesia: A randomized controlled study

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Abstract. Application of total intravenous anesthesia (TIVA) may be considered as unpractical when compared with inhalational anesthesia. Although it is mostly not recommended, mixing intravenous agents is popular in clinical practice. The aim of the present study was to investigate the suitability of using remifentanil-propofol mixture (MIXTIVA) for TIVA. Adult patients with an American Society of Anesthesiologists grade of I-II scheduled for elective thyroidectomy were randomly allocated to 3 groups (n=32 for each) to receive TIVA with remifentanil and propofol infusions separately (control group, Group I) or with MIXTIVA infusion that contained remifentanil/propofol at a proportion of 2/1,000 or 3/1,000 (remifentanil concentration, 20 or 30 μg/ml in 1% propofol in Group II or Group III, respectively). The extubation time (the primary outcome of the study), the orientation time and number of patients in whom intraoperative hypotension, hypertension or bradycardia episodes were encountered during anesthesia were comparable among the groups. The mean remifentanil infusion rate in Group III was significantly higher than that in the other groups. The mean propofol infusion rates and mean bispectral index (BIS) scores during anesthesia were comparable among groups. Hypotension accompanied with a high BIS was encountered in one patient in Group III. In conclusion, compared to the standard TIVA technique using separate drug infusions, MIXTIVA infusion used for thyroidectomies did not result in any statistically significant difference in recovery and clinical outcomes. This technique may be considered as a practical implementation for busy ambulatory centers performing general anesthesia. The present study was retrospectively registered at clinicaltrials.gov (trial registration no. NCT04394897).

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Introduction

The advantages of total intravenous anesthesia (TIVA) over inhalational anesthesia are well recognized (1). However, the use of TIVA during daily clinical practice is limited in certain instances. The application of TIVA may be considered as unpractical when compared with inhalational anesthesia. Preparation of the drugs for infusion may be time-consuming and in addition, TIVA requires infusion pumps, infusion sets and connecting tubes that increase the cost. The management of infusion rates during anesthesia maintenance is not straightforward when converting 'μg/kg/min' or 'mg/kg/h' to 'ml/h'.

Remifentanil and propofol are commonly used for TIVA due to their characteristics of ease of titration, as well as rapid onset and offset of action. It may be more appropriate to use remifentanil and propofol with target-controlled infusion (or 'smart') pumps and monitoring using processed electroencephalographic signals, but access to such devices is limited. In general practice, remifentanil and propofol infusions are usually adjusted according to clinical signs of depth of anesthesia with the guidance of manual infusion schemes that have been proposed to maintain a constant blood concentration during anesthesia, depending on the pharmacokinetics (2).

As a practical implementation for TIVA, using remifentanil and propofol as a mixture at proper concentrations allows managing one infusion instead of two and has been described in the literature (1,3-18) and certain textbooks (19-22) and has been suggested by various institutes (23-25). Studies on the stability and compatibility of drugs in the remifentanil-propofol mixture (MIXTIVA) are conflicting (26,27). However, in clinical practice, there may be other possible drawbacks of this technique: When infusing drugs as a mixture, when it is intended to administer one drug at a certain infusion rate,

the other drug may be overdosed or its blood concentration may not reach the therapeutic level. The aim of the present study was to investigate the applicability and possible disadvantages of MIXTIVA infusion for the maintenance of TIVA and the changes in clinical outcomes when compared with the standard technique using propofol and remifentanil infusions separately.

Materials and methods

Patients. The present prospective randomized controlled trial was performed at Bezmialem Vakıf University Medical Faculty (Istanbul, Turkey) between January 2013 and April 2014. After approval by the Bezmialem Vakif University Ethics Committee (reference no. 71306642/050-01-04), patients aged 18-65 years scheduled for elective thyroidectomy and with an American Society of Anesthesiologists (ASA) physical status of I or II were included in the present study. The exclusion criteria were as follows: ASA physical status of III or above; a body mass index >35 kg/m^2; pregnant, breast-feeding or menstruating females; patients who were not euthyroid; uncontrolled hypertension; hepatic, renal or cardiac insufficiency; alcohol, opioid or drug abuse; allergy or contraindication to any of the study drugs. Investigators MB and UT recruited the patients and written informed consent was obtained from each patient prior to randomization.

Drug preparation. Remifentanil (Ultiva; GlaxoSmithKline) was diluted with sterile water and the concentration of the reconstituted solution was 1 mg/ml. The remifentanil-propofol mixture MIXTIVA was prepared in a 50-ml bottle of propofol 1% (Fresenius Kabi) by adding either 1 or 1.5 mg of remifentanil to achieve a remifentanil concentration of 20 or 30 μg/ml and a remifentanil/propofol proportion of 2/1,000 or 3/1,000, respectively. Mixtures were always prepared immediately prior to administration, checked for visual stability to verify that they exhibited no evidence of precipitation or separation and used within 2 h of preparation. All infusions were administered with an Alaris GW Volumetric Pump (Cardinal Health) using an Alaris infusion set.

Randomization and blinding. Patients were randomly allocated to 3 groups to either receive anesthesia maintenance with remifentanil and propofol infusions separately (control group, Group I) or with MIXTIVA infusion with a remifentanil/propofol proportion of 2/1,000 or 3/1,000 (Group II or Group III, respectively). Simple randomization was performed using 96 opaque sealed envelopes, 32 for each group, indicating group assignments. Prior to anesthesia induction, an anesthesiologist (TU) opened the next envelope and prepared the study medications. This anesthesiologist was not involved in preoperative and postoperative data collection or anesthesia management of the patients. Resident anesthesiologists (EYG and HU) who were blinded to the study groups (Group II and III) performed all procedures.

Surgical preparation of patients. Patients received all of their regular medications on the morning of surgery. On arrival at the operating room, ECG, noninvasive blood pressure (at the ankle), pulse oximetry, temperature and bispectral index (BIS; Aspect Medical Systems) monitoring were applied. After premedication with intravenous (i.v.) midazolam (0.03 mg/kg), baseline heart rate and mean arterial blood pressure (MAP) values, were determined as the average of three consecutive measurements. Noninvasive blood pressure (NIBP) was assessed with intervals at least 3 min during anesthesia and BIS scores at the time of NIBP measurements were automatically recorded. An intravenous crystalloid solution (Isolyte-S; Koçak Farma İlaç ve Kimya Sanayi A.Ş) was administered as a 5-ml/kg bolus prior to induction and infusion at 5 ml/kg/h was started.

Anesthesia. Induction of anesthesia was as follows: In Group I, remifentanil (30 μg/ml) and propofol 1% were prepared for infusion separately and both started at 0.5 ml/kg/h. In Group II and III, MIXTIVA infusion at 0.5 ml/kg/h was started. All patients received lidocaine 1 mg/kg, propofol 1.5 mg/kg and vecuronium 0.1 mg/kg. At the 4th min of infusions, intubation was performed.

For anesthesia maintenance, in Group I, remifentanil infusion was adjusted to maintain the MAP within ±20% of the baseline value (preferably under the baseline value) and the propofol infusion rate was adjusted to maintain the BIS between 30 and 50 (target: 40). In Group II and III, the primary goal of anesthesia management was to maintain the MAP within ±20% of the baseline value (preferably under the baseline value) by adjusting MIXTIVA infusion between 0.3-1.2 ml/kg/h (dose chart for MIXTIVA infusion is provided in Table I). When the MAP was above the baseline value, MIXTIVA infusion was increased with a 0.5-1 ml bolus administration. When the MAP was within ±20% of the baseline value, the secondary goal was to maintain BIS values between 30 and 50 (target: 40). Intravenous crystalloid infusion was also adjusted to maintain the MAP within the desired levels.

In case of hypotension (defined as MAP <60 mmHg), anesthesia infusions were decreased or stopped for 1-2 min, i.v. bolus crystalloid infusion 3-5 ml/kg was administered and if hypotension persisted in two consecutive measurements, norepinephrine 5-10 μg was administered. When hypotension was accompanied with BIS values >60, ketamine 20-30 mg was administered. In case of hypertension (defined as systolic arterial pressure ≥150 mmHg persisting in two consecutive measurements despite maximum infusion rates), a bolus dose of 0.1-0.2 mg nitroglycerine was administered i.v. Bradycardia (heart rate <45 bpm) was treated with atropine 0.5-1 mg i.v.

The lungs were mechanically ventilated with a mixture of oxygen and air (fraction of inspired O_2, 50%; tidal volume, 6-8 ml/kg; respiratory rate, 10-14/min) to obtain an end-tidal CO_2 value between 30 and 35 mmHg.

Other medications. All patients received intravenous dexamethasone 8 mg, metoclopramide 10 mg, ranitidine 50 mg and dexketoprophen trometamol 50 mg after anesthesia induction; tramadol 100 mg and paracetamol 1 g, 15 min before the end of surgery. In addition, skin infiltration with lidocaine 2% was achieved prior to surgical incision. Additional vecuronium was preferably not used after the induction dose to retain the option of recurrent laryngeal nerve monitoring. All infusions were terminated during skin closure and residual neuromuscular

Table I. Dose chart for remifentanil-propofol mixture (MIXTIVA).

Infusion rate, ml/kg/h	Infusion rate[a], ml/h	Propofol[b] dose, μg/kg/min (mg/kg/h)	Remifentanil[c] dose, μg/kg/min	Remifentanil[d] dose, μg/kg/min
1.2	84	200 (12)	0.4	0.6
1	70	166 (10)	0.33	0.5
0.8	56	133 (8)	0.26	0.4
0.6	42	100 (6)	0.2	0.3
0.5	35	83 (5)	0.17	0.25
0.4	28	66 (4)	0.13	0.2
0.3	21	50 (3)	0.1	0.15

[a]Example calculated for a patient weighing 70 kg. [b]Given as 1% solution. [c]Given as 20 μg/ml solution. [d]Given as 30 μg/ml solution.

Table II. Demographic characteristics of patients.

Item	Group I (n=32)	Group II (n=32)	Group III (n=32)	P-value
Sex (male/female)	6/26	7/25	4/28	NS
Age (years)	44.6±11.4 (40.5-48.7)	46.1±10.8 (42.2-50)	42.4±11.6 (38.3-46.6)	NS
Body weight (kg)	76.3±16 (70.5-82.1)	74.4±15.6 (68.8-80.1)	71.7±14 (66.6-76.7)	NS
Body height (m)	1.65±0.09 (1.62-1.68)	1.65±0.08 (1.62-1.68)	1.65±0.07 (1.63-1.68)	NS
BMI (kg/cm^2)	28±4.8 (26.2-29.7)	27.3±4.6 (25.6-29)	26.2±4.2 (24.7-27.7)	NS
ASA I/II	25/7	26/6	29/3	NS

Values are expressed as the mean ± standard deviation (95% confidence interval) or absolute number of patients. BMI, body mass index; ASA, American Society of Anesthesiologists; NS, not significant (P>0.05).

blockade was antagonized with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Design of the study. To determine the proportions of the drugs for the mixtures, a pilot study was performed with 10 patients who underwent thyroidectomy with TIVA using remifentanil and propofol infusions separately (the same anesthesia protocol in the control group). The mean infusion rates for remifentanil and propofol were 0.26±0.09 and 81±23 μg/kg/min, respectively. The proportion of total drug consumptions for remifentanil and propofol was 3.2/1,000 in the pilot study, which was supposed to be compared with the routine management at our institution using a drug proportion of 2/1,000.

Statistical analysis. The primary outcome measure was the extubation time after all infusions were stopped. The sample size requirement was based on the preliminary data from the pilot study in which the extubation time was 8±2.4 min. Thus, at an alpha risk of 0.05, 32 patients per group would provide 80% statistical power and detect a 50% difference in extubation time. Secondary outcome measures were the incidence of undesirable events (e.g. hypotension, hypertension, bradycardia, intraoperative movement of the patient).

One-way ANOVA for parametric variables and the Kruskal-Wallis test for non-parametric variables were used. The chi-squared test was used for comparison of adverse effects. The Tukey-Kramer test was used to compare groups individually. All statistical analyses were performed using the commercially available SPSS v.16.0 software package (SPSS Inc.). P<0.05 was considered to indicate statistical significance.

Results

Enrollment. Of the 146 patients approached, 24 did not meet the criteria for inclusion, 23 refused to participate in the study and the protocol was incorrectly applied in 3, leaving 96 patients suitable to be enrolled in the present trial (Fig. 1).

Demographic characteristics. Data of demographic characteristics of patients are presented in Table II. The age and sex distribution of the patients and other patient characteristics were not significantly different between the groups.

Anesthesia characteristics. While the duration of anesthesia and surgery and the mean propofol infusion rate (total propofol consumption/body weight/infusion time) were comparable between the groups, the mean remifentanil infusion rate (total remifentanil consumption/body weight/infusion time) in Group III was significantly higher when compared with that in the other groups (P<0.05). The primary outcome of the study (the extubation time) was comparable among the groups (Table III).

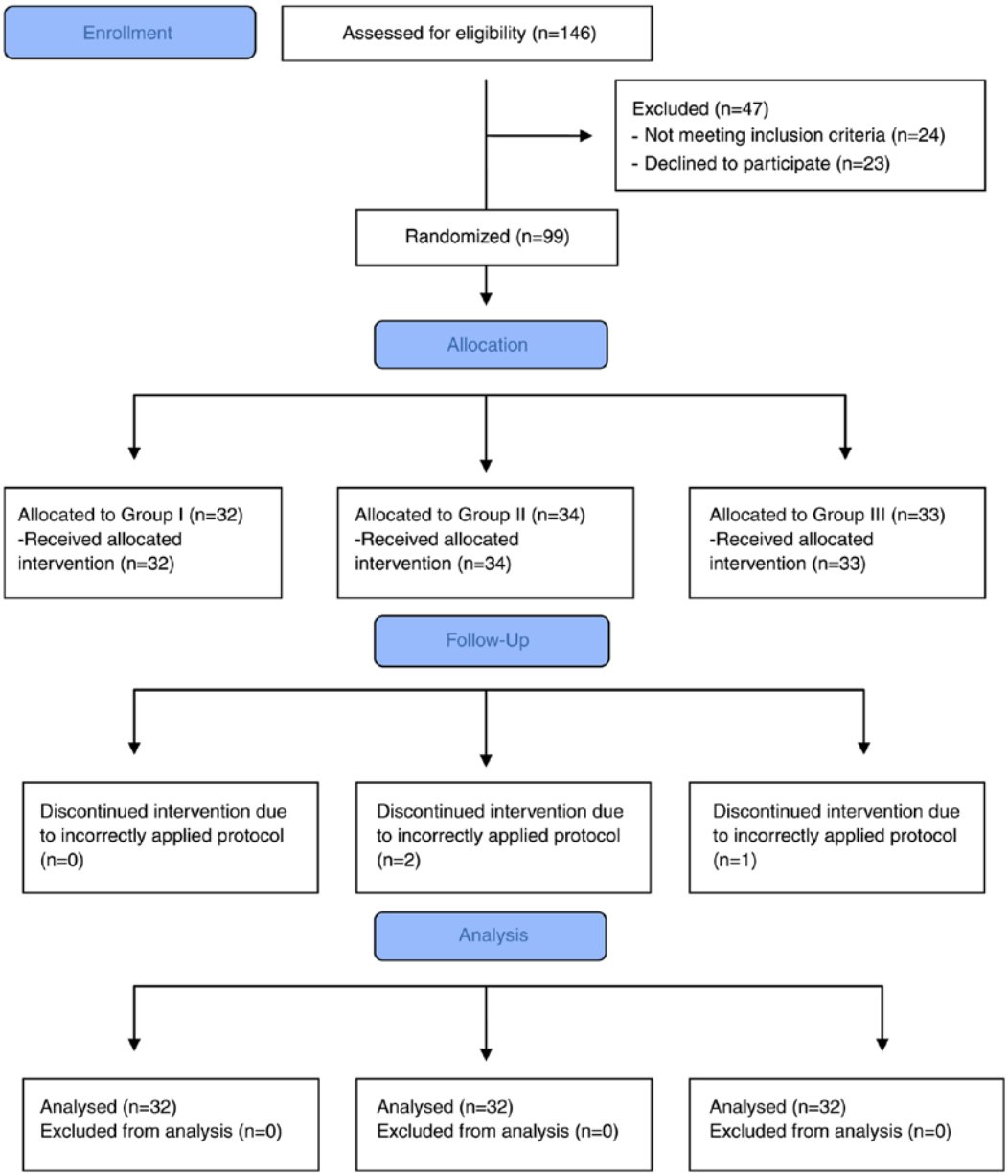

Figure 1. Flow chart of the movement of the participants through each stage of randomization.

Hemodynamics. The numbers of patients in whom intraoperative hypotension, hypertension or bradycardia episodes were encountered during anesthesia were comparable among the groups (Table III). Hypotension episodes were mostly encountered after induction or prior to delayed surgery. Hypertension episodes mostly occurred after endotracheal intubation or at the beginning of delayed surgery.

BIS scores and recovery characteristics. The mean BIS scores (the average of values recorded during anesthesia) and recovery characteristics (extubation and orientation time) of the patients were comparable among groups (Table III). The numbers of patients who had a BIS >60 recorded during anesthesia were also comparable (in most of them, BIS was between 60 and 65). A high BIS was mostly encountered after endotracheal intubation or at the beginning of delayed surgery. Hypotension accompanied with a high BIS (up to 70) was encountered in one patient in Group III who was treated with norepinephrine and ketamine (Table III). No intraoperative awareness was noted in any of the groups.

Other adverse events. In addition, no serious respiratory adverse event leading to desaturation (peripheral oxygen saturation <90% lasting >1 min) was noted in any of the groups. The incidence of postoperative nausea and vomiting, which required ondansetron administration, and shivering, which required meperidine administration, were also comparable between groups (Table III).

Discussion

In the present study, TIVA with MIXTIVA (remifentanil/propofol proportion of 2/1,000 or 3/1,000) using a single-infusion technique was not associated with any statistically significant difference in clinical outcomes (recovery characteristics, incidence of hemodynamic fluctuations and

Table III. Anesthesia characteristics.

Item	Group I (n=32)	Group II (n=32)	Group III (n=32)	P-value
Duration of anesthesia (min)	103 (100-131)	114 (101-122)	107 (96-114)	NS
Duration of surgery (min)	90 (88-119)	103 (88-108)	92 (82-100)	NS
Mean propofol infusion rate (μg/kg/min)	88±25 (79-98)	106±25 (97-115)	100±41 (85-115)	NS
Mean remifentanil infusion rate (μg/kg/min)	0.25±0.09 (0.22-0.29)	0.21±0.05 (0.19-0.23)	0.31±0.11[a] (0.27-0.35)	<0.0001
Mean BIS value	41±5 (39-42)	39±6 (37-42)	42±5 (40-44)	NS
Extubation time (min)	8 (7.2-10.2)	8.5 (7.7-10.2)	9.5 (8.4-10.8)	NS
Orientation time (min)	9 (8.6-11.8)	10 (9-11.8)	11 (9.9-12.8)	NS
Intraoperative bradycardia	1 (3)	1 (3)	0 (0)	NS
Intraoperative hypertension	5 (16)	6 (19)	2 (6)	NS
Intraoperative hypotension	7 (22)	6 (19)	5 (16)	NS
Sympathomimetic use	3 (9)	1 (3)	2 (6)	NS
Intraoperative movement	3 (9)	2 (6)	0 (0)	NS
Additional vecuronium	4 (13)	3 (9)	2 (6)	NS
Recorded BIS >60	7 (22)	6 (19)	9 (28)	NS
Ketamine use	0 (0)	0 (0)	1 (3)	NS
PONV	3 (9)	2 (6)	3 (9)	NS
Postoperative shivering	2 (6)	2 (6)	3 (9)	NS

[a]Statistically significant when compared with Group I and II. Values are expressed as the mean ± standard deviation or median (95% confidence interval) and absolute number of patients (percentage). NS, not significant (P>0.05); BIS, bispectral index score; PONV, postoperative nausea and vomiting.

other undesirable events) when compared with the standard TIVA technique using separate drug infusions.

Recently, Bagshaw *et al* (3) evaluated 873 pediatric patients who underwent mostly gastroenterology and ear, nose and throat procedures using MIXTIVA infusion. The incidence of serious adverse events such as desaturation, apnea, abdominal/chest rigidity, cough requiring paralysis, ventilatory problems and hypotension was 1.7% and they had occurred mostly at induction and were not attributed directly to the use of the mixture itself.

Although it is mostly not recommended, mixing intravenous agents appears to be popular in clinical practice. Propofol is frequently mixed with lidocaine to minimize the injection pain. Mixtures of alfentanil and propofol were used for TIVA before remifentanil became more popular (28,29). Mixtures of ketamine and propofol, 'ketofol', was recommended, particularly for sedation and analgesia for short and painful procedures (30-32). Mixtures of propofol with other intravenous drugs such as thiopental (33), ephedrine (34), methohexital (35) and metoclopramide (36), and mixtures of remifentanil with tramadol (37) have been reported, but most of these implementations may be considered as 'experimental'.

In the literature, remifentanil-propofol mixture has been used mostly for patient-controlled sedation (9,10,12,17) or deep sedation with spontaneous ventilation (5-8,11,13,14,16,18,19). Research on the use of MIXTIVA for maintenance of general anesthesia is limited (1,3,15,20,22). While certain recommendations have been given for MIXTIVA usage in general anesthesia (23-25), the remifentanil/propofol proportion varies (0.5/1,000 to 5/1,000) among centers and the possible drawbacks of this technique and optimum proportion of drugs remain to be investigated.

Stewart *et al* (26) demonstrated that remifentanil and propofol may be mixed in polypropylene syringes and used for up to 36 h when the remifentanil/propofol proportion was 5/1,000. However, when polyvinylchloride bags and lower concentrations of remifentanil were used (0.5/1,000), the duration of stability was decreased to 1 h. O'Connor *et al* (27) reported that when remifentanil solution and propofol emulsion were mixed in the same syringe, separation and layering of the drugs may result in significant differences of drug concentrations at the top and bottom of the syringe (remifentanil having a greater concentration at the top and propofol having a greater concentration at the bottom of the syringe). The lack of control groups (drugs also had to be evaluated separately without mixing) may be the major limitation of that study. In addition, they measured drug concentrations at the top and bottom of vertically mounted syringes, while in most of the syringe infusion pumps in clinical use, syringes are mounted horizontally and the drug mixture exits the syringe from the midpoint of the mixture instead of the bottom. In the present study, volumetric pumps were used and the mixtures were prepared immediately prior to infusion in 50-ml glass bottles of propofol instead of polypropylene syringes and mixtures were used within <2 h.

The use of MIXTIVA infusion may be recommended to clinicians after gaining experience with the standard TIVA technique using separate drug infusions and administrating propofol infusion with the guidance of BIS monitoring. In clinical practice, BIS monitoring is not common and in order to decrease the risk of awareness and recall during

TIVA, premedication with midazolam, adding ketamine 0.3-0.5 mg/kg to the anesthesia protocol and (as the movement of the patient under general anesthesia constitutes a warning of rising consciousness or pain) minimizing the use of neuromuscular blocking agents (NMBAs) during TIVA are recommended. General anesthesia for short procedures using a laryngeal mask airway without NMBAs appears to be best suited for MIXTIVA technique. Adjusting the remifentanil/propofol proportion of MIXTIVA according to the type of surgery (increasing the proportion for more painful procedures or hypotensive anesthesia) or to the condition of the patient (decreasing the proportion in elderly patients) may be favorable. According to the pharmacokinetics of propofol, for a constant blood or effect-site concentration, a gradual decrease in the initial propofol infusion rate is required (2). For long procedures (>2 h), it may be preferred to gradually increase the proportion, starting with 2/1,000 in the first 50 ml (with or without ketamine administration) and continuing with 3-4/1,000 in the following.

The primary outcome of the recent study was the extubation time and sample size estimation was performed according to this outcome. As a consequence, the study may be underpowered to obtain any differences in other clinical outcomes. In addition, a 'BIS-blinded' study would be more appropriate to determine the risk of awareness.

In conclusion, compared with the standard TIVA technique using separate drug infusions, when TIVA, using a single-infusion technique with MIXTIVA (remifentanil/propofol proportion, 2/1,000 or 3/1,000) was applied for thyroidectomies, no statistically significant difference in recovery and clinical outcome was obtained. This technique may be considered as a practical implementation for busy ambulatory surgery centers performing general anesthesia. Adjustment of the remifentanil-propofol proportion for different types of surgery and patient groups must be considered and further studies with larger patient populations are warranted.

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Availability of data and materials

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

Authors' contributions

MB designed the study. MB and TU were involved in performing the study procedures, data analysis and writing of the manuscript. UT contributed to data analysis and writing of the manuscript. EYG and HU were involved in performing the study procedures and data analysis. EO contributed to design of the study and was involved in writing the manuscript. All authors confirm the authenticity of the raw data, and read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Bezmialem Vakif University (Istanbul, Turkey; reference no. 71306642/050-01-04). Informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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