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Pre-administration of remifentanil in target-controlled propofol and remifentanil anesthesia prolongs anesthesia induction in neurosurgical patients

A double-blind randomized controlled trial

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Abstract

Background: Pre- and co-administration of remifentanil in target-controlled propofol and remifentanil anesthesia are the most common methods in clinical practice. However, anesthesia induction time by timing remifentanil administration was not identified. Therefore, we investigated the induction time of anesthesia based on type of remifentanil administration in target-controlled anesthesia.

Methods: A total of 60 patients were randomly assigned to 1 of 2 groups: Pre-administered with remifentanil before propofol infusion (Group R, n = 30) and co-administered with remifentanil with propofol (Group N, n = 30). The primary outcome was total induction time based on the order of remifentanil administration. Secondary outcomes were from start of the propofol infusion time to loss of consciousness (LOC), rocuronium onset time, time to Bispectral index (BIS) 60, and hemodynamic variables.

Results: The mean ± SD of total induction time was 180.5 ± 49.0 s in Group N and 246.3 ± 64.7 s in Group R (mean difference: 65.8 seconds; 95% CI: 35.0–96.5 s, $P < .01$). Time to BIS 60 and rocuronium onset time were longer in the Group R ($P < .01$ and $P < .01$, respectively). The Δheart rate and Δcardiac output values were lower in the Group R ($P = .02$ and $P = .04$, respectively). Injection pain was reported by 11 of 28 (39%) in the Group N and in 2 of 28 (7%) in the Group R (difference in proportion: 32%, 95% CI: 10–51%, $P = .01$).

Conclusion: Pre-administration of remifentanil in target-controlled propofol and remifentanil anesthesia prolongs total induction time about 35% compared to co-administration of remifentanil and propofol by decreased CO.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = Bispectral index, Ce = target effect-site concentration, CI = confidence interval, CO = cardiac output, HR = heart rate, IQR = interquartile range, LOC= loss of consciousness, MAP = mean arterial pressure, MD = mean difference, mean changes Δ = mean change, PONV = postoperative nausea vomiting, SV = stroke volume, SVR = systemic vascular resistance, SVV = stroke volume variation, TCI = target controlled infusion, TOF = train-of-four.

Keywords: induction time, neurosurgery, propofol, remifentanil, target-controlled anesthesia

1. Introduction

Target controlled infusion (TCI) is commonly used in neurosurgery because of reduced perioperative stress response, reduced acute systemic inflammatory response, rapid recovery, and decreased postoperative nausea vomiting (PONV) compared with more volatile anesthesia.[1–3] Propofol is advantageous in neurosurgery because it can reduce cerebral blood volume and intracranial pressure and preserve both autoregulation and vascular reactivity.[4] In addition, remifentanil may have a neuroprotective effect that suppresses cell death by lowering the expression of TNF-α and TNFR1 proteins, which is beneficial for perioperative brain protection.[5–7]

Generally, pre- and co-administration of remifentanil and propofol in TCI are the most common methods in clinical practice.[8] Several studies have assessed timing of remifentanil administration.[8–11] Propofol administration prior to remifentanil suppressed remifentanil induced cough,[9] whereas pre-administration of remifentanil reduced the injection pain of propofol.[10] In addition, the administration sequence of propofol

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JHA and DK contributed equally to this study.

The authors report no conflicts of interest.

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and remifentanil does not influence the ED50 and ED95 of rocuronium,[8] but the pre-administration of remifentanil prolonged the rocuronium onset time, which was due to decreased cardiac output (CO) by remifentanil.[11] Although there are many clinical pharmacological approaches depending on the timing of administration of remifentanil,[8,11,12] there is no study on the effect of remifentanil on induction time.

Generally, combination of hypnotic-sedative agents such as propofol and opioid such as remifentanil is known to have a synergic effect.[13] However, the induction time of anesthesia based on the timing of remifentanil administration in target-controlled propofol and remifentanil anesthesia has not been identified. We hypothesized that the pre-administration of remifentanil would maximize synergy effect and reduce the anesthetic induction time. Therefore, we conducted a prospective, randomized, double-blinded study to compare the induction time of anesthesia by pre- and co-administration of remifentanil in target-controlled propofol and remifentanil anesthesia in neurosurgical patients.

2. Materials and methods

This prospective, double-blinded, randomized study was approved by the Institutional Review Board (Samsung Medical Center, South Korea, IRB No. 2017-12-091, Jan 12, 2018) and the study design was registered in the Clinical Trial Registry of Korea (KCT0002733; Principle Investigator, J.S.J; date of registration, Jan 17, 2018). All patients participated in the study after providing written informed consent. This study included American Society of Anesthesiologists (ASA) I-II patients (between 19 years and 75 years of age) scheduled for elective neurosurgery that were under general anesthesia from January 2018 to April 2018 at the Samsung Medical Center, Seoul, Korea. Exclusion criteria included age <18 years, expected difficult airway, body mass index >30 or <18.5 kg/m^2, neuromuscular disease, mental disorder, metabolic disorder, asthma, chronic obstructive pulmonary disease, cardiovascular disease (including hypertension), renal disease, pregnancy, and opioid use before surgery. The study participants were randomly assigned to 1 of 2 groups using a randomized list designed by the statistics team of our center: pre-administration of remifentanil before propofol infusion (Group R) or co-administration of remifentanil with propofol (Group N).

2.1. Study design and data collection

Three syringe pumps (Injectomat TIVA Agilia, Fresenius KABI, France) in TCI mode were prepared. For each syringe pump, propofol (Fresofol 2% inj., 50 ml vial, Fresenius Kabi, Oberosterreich, Austria) was prepared in a 50 ml syringe, 20 ml of remifentanil (Ultiva^{TM} inj., 1 mg vial, GlaxoSmithKline, Rixensart, Belgium) was diluted with normal saline at a concentration of 50 μg/ml, and normal saline in a 20 ml syringe for blinding was prepared. The 2 syringes not containing propofol were masked and were labeled with number 1 or 2. Group assignment was conducted using sequentially numbered, sealed opaque envelopes opened only after enrollment by one of the authors who prepared the study drugs, but was not involved in either anesthetic management or outcome assessment.

Patients did not receive premedication. Standard monitoring such as electrocardiography, pulse oximetry, noninvasive blood pressure, and Bispectral index (BIS) monitor was performed on arrival at the operating room. Before anesthesia induction, the patients underwent an awake arterial line cannulation after local anesthetic (1% lidocaine 0.5 ml) infiltration for invasive continuous arterial pressure monitoring (via FloTrac, version 1.08, Edwards Lifesciences, Irvine, CA, USA). Neuromuscular monitoring was performed with acceleromyography every 15 s using the TOF-Watch SX (Organon Ltd, Dublin, Ireland) at the adductor pollicis. Remifentanil (or normal saline) and propofol were administered by TCI pumps after preoxygenation with 100% O_2 via a facial mask. The pharmacokinetic sets used to calculate target effect-site concentrations (Ce) for propofol and remifentanil were Marsh and Minto models, respectively.[14,15] Ce was set to 4 ng/ml for remifentanil and 6 μg/ml for propofol.[9] After the first syringe (remifentanil or normal saline) reached Ce 4ng/ml, then propofol and the remaining 20cc syringe pump were administered at 6 μg /ml and 4 ng/ml, respectively. The drug administration sequences of both groups are represented in Figure 1. Loss of consciousness (LOC) was assessed every 5 s and after disappearing eyelash reflex was confirmed, 0.6 mg/kg rocuronium was injected. Intubation was performed after confirming muscle relaxation with twice train-of-four (TOF) count 0. The tracheal intubation was performed using a Macintosh laryngoscope and Cormack–Lehan grade was obtained. And, patients who are expected to have difficulty airway was used a Macintosh or Glidescope video laryngoscope (GVL; Verathon, Bothell, WA, USA) at the discretion of the practitioner. After intubation, a syringe pump was adjusted to 2 ng/ml for remifentanil and normal saline, and 4 μg/ml for propofol. Hypotension (mean arterial pressure [MAP] < 55 mmHg) was treated with 5 mg ephedrine, and bradycardia (< 50 beats/min) was treated with 0.5 mg atropine.

The investigator recorded from start of the propofol infusion time to LOC, time to BIS 60, rocuronium onset time, total induction time and hemodynamic variables such as heart rate (HR), MAP, CO, stroke volume (SV), stroke volume variation (SVV), and BIS values from the beginning of anesthesia induction to five minutes after tracheal intubation at each point, that is, before starting anesthesia induction (T0), at propofol administration (T1), at LOC and rocuronium injection (T2), at BIS 60 (T3), immediately before and immediately after intubation (T4 and T5), and at 1 min intervals after intubation (T6-T9). Modified Mallampati classification, Cormack-Lehan's grade, intubating condition[16] and complications such as cough, injection pain, and chest rigidity were also recorded.

Primary outcome was the total induction time, which was defined from propofol administration (T1) to immediately before intubation (T4). Secondary outcomes were time to LOC (from T1 to T2), time to BIS 60 (from T1 to T3), rocuronium onset time (from T2 to T4), complications, remifentanil and propofol dose during induction (from T0 to T4), and were included as variables related to hemodynamic, anesthesia, and intubation.

2.2. Statistical analysis

Based on an unpublished pilot study, we found that the mean (SD) duration of total induction time was 195 (18) sec in the Group N (n = 5) and 215 (25) in the Group R (n = 5). The sample size was calculated with a power of 0.9 and an alpha error of 0.01. At least 27 patients per group were required. Assuming a 10% dropout rate, we planned to recruit a total of 60 patients (30 subjects for each group). Continuous variables are presented as the mean (SD) or median and interquartile range (IQR), as appropriate, and categorical variables are presented as the number (percentage). Continuous variables were analyzed using

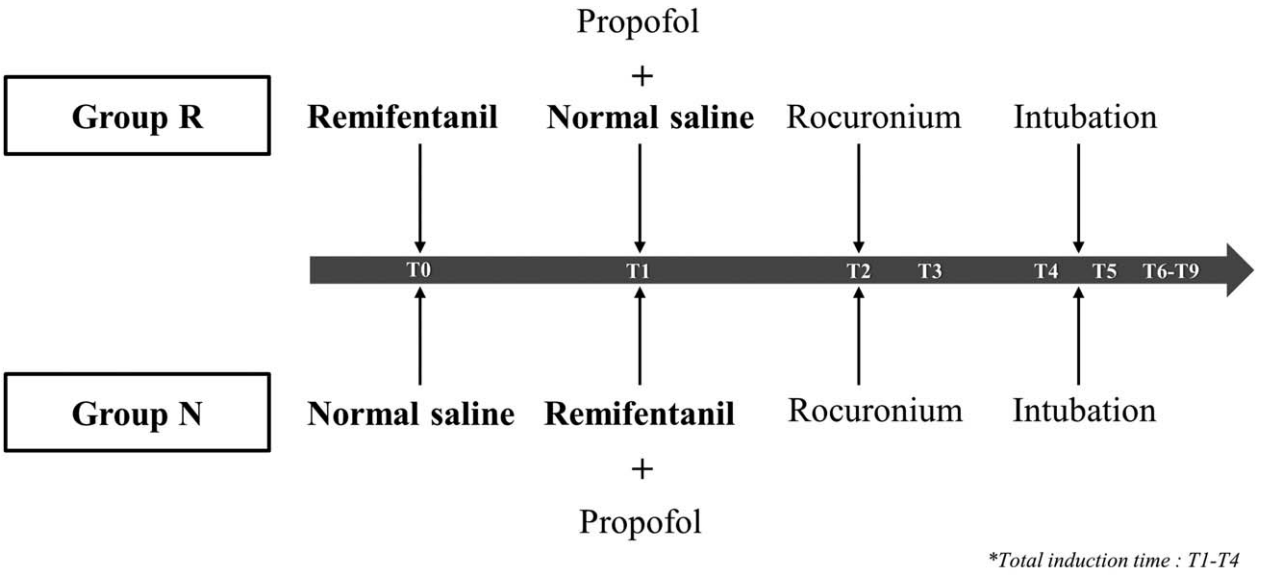

Figure 1. Study protocol drug sequence. T0, before starting anesthesia induction; T1, Propofol administration; T2, LOC and rocuronium injection; T3, BIS 60; T4 and T5, Before and immediately after intubation; T6-T9: One-minute intervals after intubation. BIS = Bispectral index.

the Student *t* test or Mann–Whitney *U* test where appropriate. Normality of continuous variables was assessed by the Kolmogorov–Smirnov test. Categorical variables were analyzed using the Pearson chi-square test or Fisher exact test, where appropriate. Hemodynamic variables, except SVV, were used to evaluate mean changes (Δ), relative to the values before starting induction of anesthesia at each time point. The differences in the hemodynamic variables between the two groups over time were analyzed by repeated measures analysis of variance, and the Student *t* test or Mann–Whitney *U* test was used to compare the values at each time point between the 2 groups. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL). A *P*-value less than .05 was considered to be statistically significant.

3. Results

A total of 60 patients were recruited and 56 patients completed the study (Fig. 2). Four patients were excluded due to technical error (n = 2) and hemodynamic instability after anesthesia induction (n = 2). Patient characteristics were not significantly different between the 2 groups (Table 1).

The variables for induction time are shown in Table 2. The total induction time was longer in Group N than in Group R ($P < .01$). The time to BIS 60 and rocuronium onset time were longer in Group N than in Group R ($P < .01$ and $P < .01$, respectively). However, the time to LOC was not significantly different between the two groups ($P = .35$). And, the remifentanil and propofol doses during induction were more in Group R than in Group N ($P < .01$ and $P < .01$, respectively).

The hemodynamic variables between the two groups, including HR, MAP, CO, SV, and SVV over time, are shown in Figure 3. There were significant differences according to group interaction for ΔHR and ΔCO ($P = .02$ and $P = .04$, respectively). However, the ΔMAP, ΔSV, and SVV were not significantly different ($P = .77$, $P = .67$ and $P = .80$, respectively). The ΔHR was significantly decreased in Group R compared to Group N at the T1, T2, and T3 ($P = .01$, $P < .01$ and $P = .05$; respectively). The ΔCO was significantly decreased in Group R compared to Group N at T1 and T2 ($P < .001$, $P = .01$; respectively).

The patient complications are shown in Table 3. Cough and chest rigidity were not significantly different between the 2 groups. However, injection pain occurred more frequently in Group N than in Group R (difference in proportion: 32%, 95% CI: 10 to 51%, $P = .01$). The variables for intubation are shown in Table 3. The Modified Mallampatti classification, Cormack–Lehan grade and intubating condition were not significantly different between the 2 groups. Rescue ephedrine was administered to 5 patients with hypotension, which were administered at T5, T6, and T9 in Group N and T7 and T9 in Group R.

4. Discussion

This randomized trial demonstrated that pre-administration of remifentanil prolonged the total induction time of 35% (66 s) compared to co-administration of remifentanil, and time to BIS value 60 and rocuronium onset time were prolonged time to BIS value 60 and rocuronium onset time. In addition, pre-administration reduces injection pain caused by propofol. In particular, the prolongation of total induction time is attributed to decreased CO and HR by pre-administration of remifentanil.

A previous study demonstrated that patients with a high CO required a large dose of propofol and took a long time to achieve hypnosis.[17,18] Although high CO levels decrease the plasma concentration of propofol, it allows fast delivery of the drug from the injection site to the target site.[19] On the other hand, low CO will have the opposite effect. In this regard, prolongation of the total induction time is associated with relatively low CO. In our study, CO was significantly decreased in Group R compared to Group N in T1 and T2, which affected onset time of rocuronium.[11,19] A previous study demonstrated that pre-administration of remifentanil prolongs the onset of rocuronium compared to post-administration of remifentanil.[11] The prolongation of rocuronium onset time was attributed to a decrease in CO, and our study also showed similar results. We compared HR, SV, and SVV, which are factors that can determine CO.

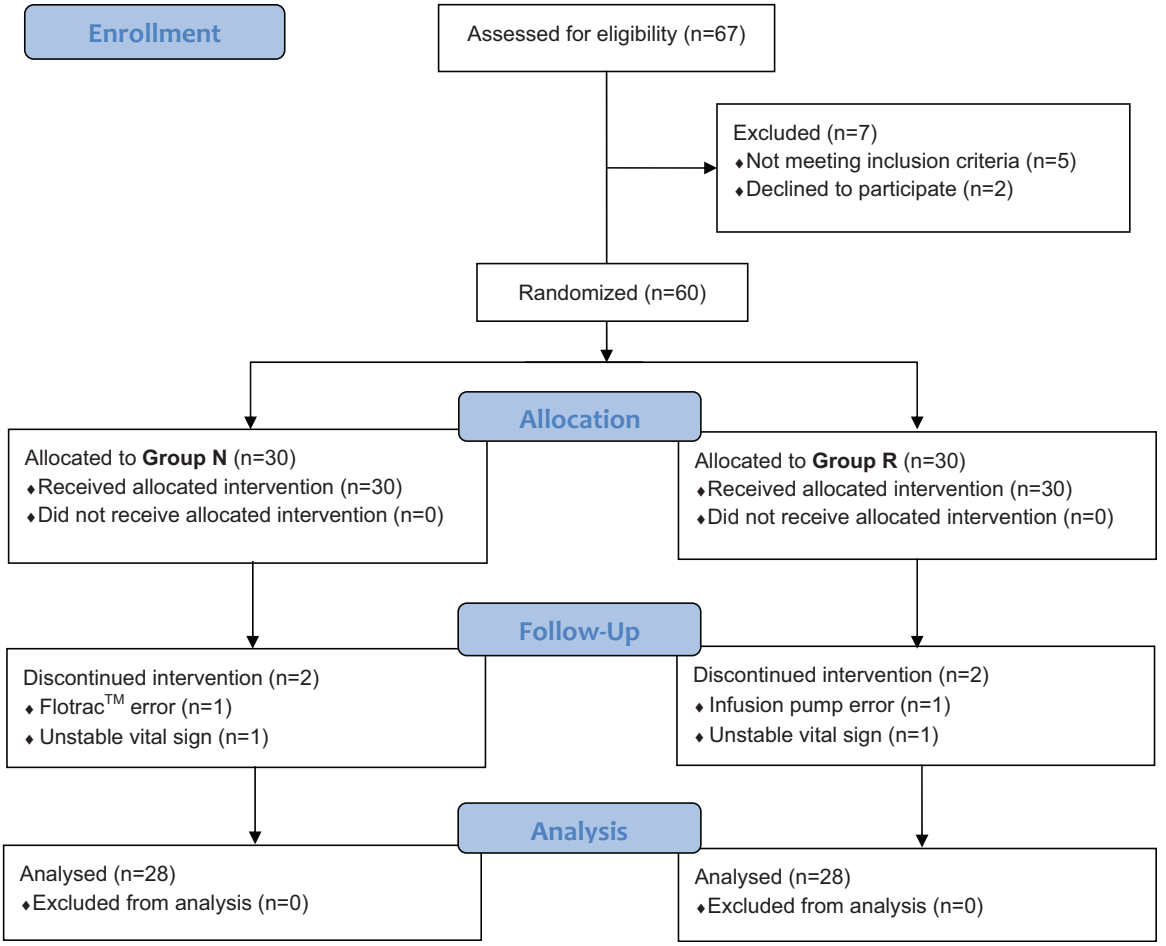

Figure 2. CONSORT flow diagram.

There were no differences in SV or SVV changes between these 2 groups, however, HR was significantly decreased in pre-administration of remifentanil. High doses of remifentanil are known to reduce HR and reduce MAP, due to inhibition of intraatrial conduction and sinus node automaticity as well as decrease in peripheral vascular tone.[20,21] In our study, MAP changes were not different between the 2 groups, but the decrease in HR was evident in the pre-administration remifentanil group. Therefore, the decrease of CO may be due to the decrease of HR due to the use of remifentanil.

The analgesic concentration of pretreatment opioids is generally known to promote propofol-induced LOC.[22] We estimated the onset time of propofol using time to LOC (achieving hypnosis) and time to BIS 60 (achieving general

Table 1

Patient characteristics.

	Group N (n=28)	Group R (n=28)	*P*
Gender (F/M)	19/9 (68/32)	12/16 (43/57)	.06
Age, years	50.3±12.0	51.8±9.9	.89
Weight, kg	62.5±10.1	67.4±14.1	.14
Height, cm	162.8±9.8	165.6±10.0	.30
BMI, kg/m^2	23.4±2.6	24.0±3.0	.32
ASA class (I/II)	19/9 (68/32)	17/11 (61/39)	.56
Type of Surgery			
Aneurysm clipping	8 (29)	5 (18)	
Brain tumor resection	5 (18)	10 (36)	
EDAS	2 (7)	1 (4)	
MVD	11 (39)	7 (25)	
TSA	2 (7)	5 (18)	

Data are expressed as the mean±SD or number (%).
ASA=American Society of Anesthesiology; BMI=body mass index; EDAS=Encephalo-duro-arterio-synangiosis; MVD=Microvascular decompression; TSA=Transsphenoidal approach.

Table 2

Anesthesia duration and administration dose of drug under induction using TCI.

Period	Group N (n=28)	Group R (n=28)	Mean difference (95% confidence interval)	*P*
Total induction time, s	180.5±49.0	246.3±64.7	65.8 (35.0 to 96.5)	<.01
Time to LOC, sec	60.5±24.2	66.6±24.3	6.1 (−6.9 to 19.1)	.35
Time to BIS 60, s	88.1±29.2	134.6±55.4	46.4 (22.7 to 70.2)	<.01
Rocuronium onset time, s	120.0±43.7	179.6±61.7	59.7 (31.0 to 88.3)	<.01
Remifentanil dose during induction, μg	80.8±10.7	110.6±11.7	29.8 (23.8 to 35.8)	<.01
Propofol dose during induction, mg	155.3±24.7	189.1±21.5	33.8 (21.4 to 46.2)	<.01

Data are expressed as the mean±SD.
BIS=bispectral index, CI=confidence interval, LOC=loss of consciousness, MD=mean difference.

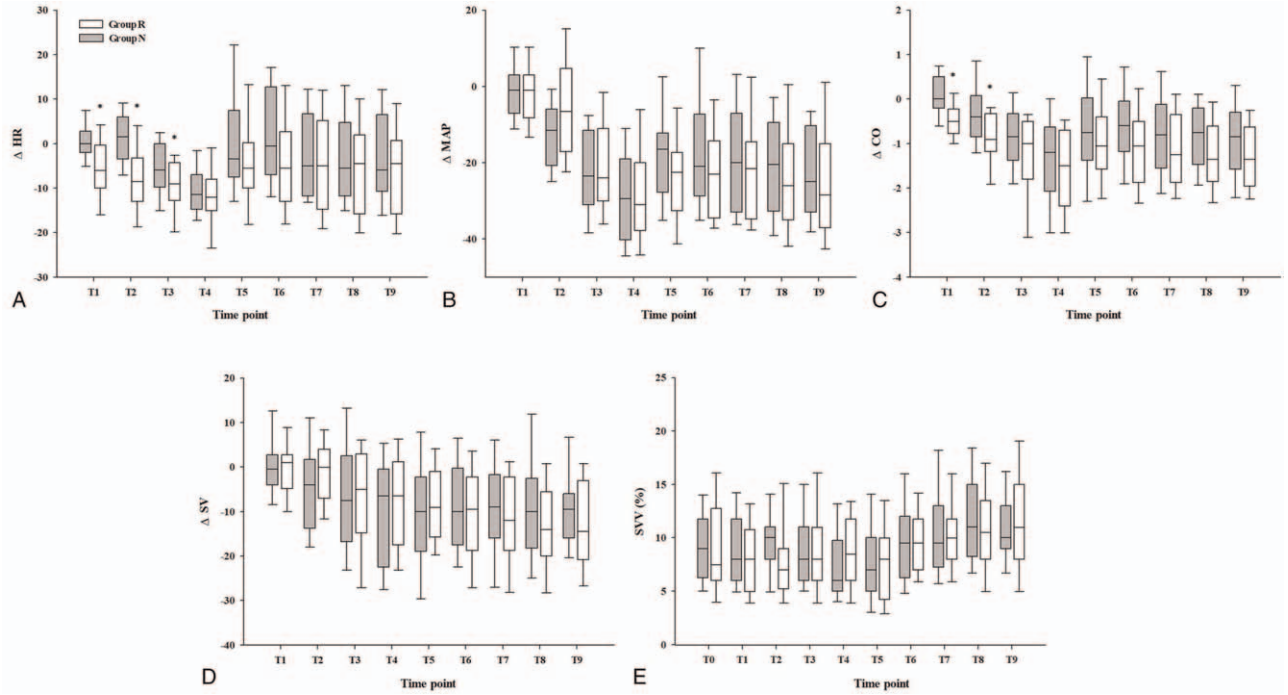

Figure 3. Mean changes relative to the values before starting anesthesia induction, Δheart rate (ΔHR, A), Δmean arterial pressure (ΔMAP, B), Δcardiac output (ΔCO, C), Δstroke volume (ΔSV, D), and stroke volume variation (SVV, E). $^{*}P < .05$ vs Group N. T0, before starting anesthesia induction; T1, Propofol administration; T2, LOC and rocuronium injection; T3, BIS 60; T4 and T5, Before and immediately after intubation; T6-T9: One-minute intervals after intubation. BIS = Bispectral index, CO = cardiac output, HR = heart rate, MAP = mean arterial pressure, SV = stroke volume, SVV = stroke volume variation.

anesthesia). Hypnosis can be measured by performing a clinical assessment and using the BIS value,[23,24] but the BIS value is not a reliable method for determining the LOC.[23] Therefore, we used a clinical assessment to confirm hypnosis. In our study, time to LOC and BIS value at LOC were not significantly different and time to BIS 60 was prolonged by 46.4 s for the pre-administration of remifentanil. This result suggests that propofol onset time also increased. Although there are numerous factors involved in human arousal, the mechanism for opioids and consciousness levels can be explained in relation to the cerebral neurotransmitter acetylcholine.[25–27] In an animal study, acetylcholine release is inhibited by fentanyl and morphine sulfate, but not in remifentanil.[26,27] In addition, propofol is associated with inhibited release of acetylcholine.[27] Therefore, the prolongation of propofol onset time may be due to the reduction of CO rather than the direct effect of remifentanil.

Table 3

Complication and airway evaluation, and intubation condition score during anesthesia induction.

	Group N (n = 28)	Group R (n = 28)	*P*
Complication			
Cough	8 (29)	5 (18)	.35
Injection pain	11 (39)	2 (7)	.01
Chest rigidity	1 (4)	4 (14)	.35
Modified Mallampati classification			.19
Class I	8 (29)	3 (10)	
Class II	14 (50)	15 (54)	
Class III	6 (21)	10 (36)	
Class IV	0 (0)	0 (0)	
Cormack Lehan's grade			.32
Grade I	11 (39)	8 (29)	
Grade III	12 (43)	9 (32)	
Grade III	4 (14)	10 (36)	
Grade IV	1 (3)	1 (3)	
Intubating condition			.60
Excellent	27 (96)	26 (93)	
Good	1 (3)	1 (3)	
Inadequate	0 (0)	1 (3)	

Data are expressed as number (%).

There are several methods for reducing injection pain associated with propofol, such as adding lidocaine to propofol, cooling or warming propofol, diluting the propofol solution, and pretreatment with an IV injection of lidocaine, ondansetron, metoclopramide, opioid, or magnesium.[10,30] Among these, the pre-administration of remifentanil is known to reduce the injection pain of propofol.[10] In our study, pre-administration of remifentanil confirmed that the incidence of injection pain associated with propofol was reduced by 32% compared to the

Intracranial pressure control is essential for rapid sequence induction in neurosurgical patients with high risk of aspiration risk. Depolarizing neuromuscular agents with rapid onset time such as succinylcholine are contraindicated due to increased intracranial pressure. Therefore, rocuronium is mainly used by non-depolarizing agents.[28] In addition, remifentanil does not affect cerebrovascular hemodynamics, such as cerebral perfusion pressure or intracranial pressure, and is commonly used with sedative drugs during rapid sequence induction.[29] Although drug selection is important for rapid sequence induction, it is also important to shorten the drug onset time and total induction time. Based on our study, total induction time may be prolonged in pre-administration of remifentanil, care should be taken in the order of drug administration during unexpected rapid sequence intubation in remifentanil and propofol anesthesia.

co-administration of remifentanil and propofol. Therefore, pre-administration of remifentanil may be more effective for reducing the injection pain associated with propofol. The mechanism for injection pain reduction can be explained by two mechanisms, central and peripheral. Opioid receptors are present at the dorsal root ganglia, the central terminals of the primary afferent nerve, and the peripheral sensory nerve fibers and their terminal.[31] The reduction of injection pain associated with propofol may be due to the interaction with the central and peripheral μ-opioid receptors of remifentanil. Meanwhile, the remifentanil infusion, using TCI, is known to cause coughing, chest tightness, and bronchial spasm.[32–34] In our study, there was no significant difference in the incidence of coughing or chest rigidity in either group. Therefore, the side effects of remifentanil may not be related to the administration sequence of remifentanil and propofol.

There were several limitations to our study. First, we did not measure plasma concentrations of remifentanil and propofol. The plasma concentrations in TCI varied during anesthesia induction,[24] and could affect the anesthesia induction time. However, since our study focused on the induction time by the sequence of drug administration, we assumed that the difference of plasma concentration on induction time could be excluded. Second, we cannot assume that the measured value of the CO using FloTrac was correct or not. In several studies, FloTrac was significantly correlated with thermodilution via a pulmonary artery catheter, which is considered to be the gold standard for measuring CO.[35,36] The change in CO due to reduction in the systemic vascular resistance (SVR) is less accurate in the third-generation FloTrac. In our study, there is a possibility of CO measurement error due to rapid decrease of SVR by administration of remifentanil, and the accuracy of CO measurement can be improved by using fourth-generation FloTrac, which has been corrected to account for such errors.[37,38] Third, there was no statistical significance associated with gender, but the male ratio was higher in pre-administration of remifentanil (16/28) than in co-administration of remifentanil and propofol (9/28). Generally, cardiac variables were higher for males than for females.[39,40] To compensate for this, we analyzed changes from baseline values at each point.

In conclusion, pre-administration of remifentanil in target-controlled propofol and remifentanil anesthesia prolongs total induction time about 35% compared to co-administration of remifentanil and propofol by decreased CO. Therefore, the anesthesiologist should be aware of prolonged anesthesia induction time due to reduction of CO on pre-administration of remifentanil and determine the order of the remifentanil based on risk and benefit.

Author contributions

Conceptualization: Jin Hee Ahn, Doyeon Kim, and Ji Seon Jeong.
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Formal analysis: Eun Kyung Lee.
Investigation: Jin Hee Ahn, Doyeon Kim, Jeong Jin Lee, and Eun Kyung Lee.
Methodology: Jin Hee Ahn, Doyeon Kim, Ik Soo Chung, and Ji Seon Jeong.
Supervision: Ik Soo Chung and Jeong Jin Lee.
Visualization: Ik Soo Chung.
Writing – original draft: Jin Hee Ahn and Ji Seon Jeong.
Writing – review & editing: Ji Seon Jeong.
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