Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(8) 3097–3103

DOI: 10.1177/0300060518772227
journals.sagepub.com/home/imr
SAGE

Optimal neuromuscular blocking effects of remifentanil during tracheal intubation under general anesthesia

So Young Kwon, Si Wook Chung and Jin Deok Joo

Abstract

Objective: This study was performed to determine the effect of the remifentanil dose on the onset time of rocuronium with electromyography.

Methods: This retrospective comparative study included 75 patients undergoing general anesthesia for elective surgery. Patients received lidocaine (40 mg) and propofol (2 mg/kg) followed by rocuronium (0.6 mg/kg) with either saline infusion (Group S), remifentanil at 0.5 μg/kg/minute (Group R 0.5), or remifentanil at 1.0 μg/kg/minute (Group R 1.0). Neuromuscular block was monitored by train-of-four (TOF) electromyography, and the times taken to reach TOF 0 and TOF ratio (TOFR) 25% were recorded.

Results: The times taken to reach TOF 0 and TOFR 25% were significantly higher in Groups R 0.5 and R 1.0 than in Group S. The time taken to reach TOF 0 was 130.0 ± 6.4 s in Group S, 142.6 ± 6.0 s in Group R 0.5, and 183.0 ± 11.6 s in Group R 1.0. The time taken to reach TOFR 25% was also higher in Groups R 0.5 and R 1.0 than in Group S.

Conclusions: As the remifentanil dose increases, the intubation time required to reach TOF 0 also increases. Remifentanil has an effect on the onset of rocuronium.

Keywords

General anesthesia, remifentanil, rocuronium, train-of-four, electromyography, neuromuscular block

Date received: 8 September 2016; accepted: 28 March 2018

Department of Anesthesiology and Pain Medicine, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Corresponding author:
Jin Deok Joo, Department of Anesthesiology and Pain Medicine, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, #93 Chi-Dong, Paldal-Ku, Suwon 442-723, Republic of Korea.
Email: joojd@catholic.ac.kr

Introduction

Endotracheal intubation increases the heart rate (HR) and blood pressure (BP) to augment sympathetic responses.[1] In general, fluctuations in vital signs during intubation do not pose a threat in normal, healthy patients. However, adjuvant medications for hemodynamic stability are mandatory to reduce morbidity and mortality rates in patients with recent myocardial infarction, coronary artery disease, and cerebrovascular disease.[2] Most anesthetics effectively attenuate this response. A previous study showed that various agents effectively modify hemodynamic changes.[3] Around the time of that study, remifentanil was a new opioid undergoing multicenter clinical trials. Remifentanil is rapidly metabolized by nonspecific esterases in plasma and tissue; therefore, its half-life is short and onset time is rapid, similar to alfentanil. Because of remifentanil's rapid onset and ability to offset opioids, it has recently become more commonly used as adjuvant anesthetic for tracheal intubation to attenuate hemodynamic responses.[4,5] The differential dose of rocuronium and the fixed dose of remifentanil are associated with the timing and conditions of intubation.[5]

However, the effects of these various agents on neuromuscular blockade have not been fully elucidated. A few studies have shown the effects of adjuvants on neuromuscular blockade.[6–8] One study revealed the effects of fentanyl, remifentanil, and dexmedetomidine on neuromuscular blockade.[6]

The present study was performed to determine the effect of remifentanil on the time to reach optimal neuromuscular blockade for tracheal intubation under monitoring with train-of-four (TOF) electromyography.

Patients and methods

Patients

This was a prospective randomized case control study. The Institutional Review Board of The Catholic University of Korea, Suwon, Republic of Korea approved the study protocol (VC 12MISI0141).

After obtaining written informed consent, we enrolled adult patients who were scheduled for elective surgery. Patients with a history of cardiac, pulmonary, renal, hepatic, cerebral, or neuromuscular disease; an allergy to propofol or opioids; chronic alcohol or drug abuse; a body mass index of >30 kg/m^2; or pregnancy were excluded from this study.

Anesthesia

Upon arrival in the operating room, we applied standard monitoring including pulse oximetry, electrocardiography, HR measurement, end-tidal carbon dioxide measurement, and noninvasive monitoring of arterial BP. Neuromuscular transmission was monitored by TOF electromyography in accordance with the guidelines for good clinical research practice.[9] Responses to stimulation of the ulnar nerve were measured at the first dorsal interosseous muscle as described below.

After baseline measurements, the patients were randomly categorized into one of three groups using a computer program. Patients in Group R 0.5 received remifentanil at 0.5 μg/kg/minute, those in Group R 1.0 received remifentanil at 1.0 μg/kg/minute, and those in Group S received saline. The study solution consisted of either 2 mg of remifentanil diluted in a total volume of 100 mL of 0.9% sodium chloride or only 100 mL of 0.9%

sodium chloride. The patients and physicians were blinded to the randomization process.

In all patients, general anesthesia was induced with 40 mg of lidocaine to prevent propofol infusion pain followed by infusion of 2 mg/kg of propofol over 30 s. After loss of the eyelash reflex, 0.6 mg/kg of rocuronium bromide was administered, and a continuous infusion of remifentanil was started through a 20-gauge venous cannula on the forearm. The 95% effective dose of rocuronium is 0.3 mg/kg;[10] for the present study, we used twice this dose (0.6 mg/kg).

Protocol

Neuromuscular blockade was monitored on the opposite forearm with intravenous access. It was assessed by stimulation of the ulnar nerve and recording of acceleromyographic responses using transcutaneous Ag/AgCl electrodes with TOF-Watch SX (Organon Ltd., Dublin, Ireland). The baseline stabilization and calibration sequence were performed immediately after loss of the patient's eyelash reflex. The automatic calibration procedure started with a 50-mA current to supramaximal stimulation. After confirming the calibration, the stimulus was changed to a TOF pattern at 2 Hz every 10 s. We recorded the time required to reach a TOF ratio (TOFR) of 25% (T_{25}) and TOF score of 0 (T_0).

We estimated the differential mean BP (MBP) and HR using the following equation: Differential MBP (HR) = Baseline MPB (HR) – T_0 MBP (HR).

Statistical analyses

All data are presented as mean ± standard deviation. A previous study showed that the optimal intubation time is 136 ± 35 s.[5] Calculation of the sample size was based on preliminary data, $\alpha = 0.05$, power of 80%, three groups, effect size = 0.40, and, if the present study results were statistically significant, F (2.63) = 3.14. G*Power analysis showed that a sample size of 25 patients per group was needed. Paired and unpaired Student's t tests and one- and two-way repeated-measures analysis of variance (ANOVA) were used to compare measurements within groups. The statistical analysis and sample size determination were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

After application of the inclusion criteria, 75 patients ranging in age from 18 to 60 years with an American Society of Anesthesiologists (ASA) physical status of I or II were enrolled. All patients completed the study protocol. Demographic data were similar among the three groups of patients (Table 1). Sex, age, height, weight, and body mass index did not differ among the groups. Group R 0.5, Group R 1.0, and Group S comprised 25 patients each.

Comparison of the mean onset time of neuromuscular block among the three groups revealed that the time to reach T_0 and T_{25} was longer in Groups R 0.5 and R 1.0 than in Group S (Table 2); one-way ANOVA showed a significant difference among the groups ($P < 0.001$). In Group S, the time to reach T_0 and T_{25} was 130.0 ± 6.4 and 96.5 ± 6.4 s, respectively. The onset time of TOF was significantly lower in Group S than in Groups R 0.5 and R 1.0 ($P < 0.001$).

The changes in MBP and HR are shown in Figures 1 and 2. Two-way ANOVA

Table 1. Demographic data in the three study groups

	Group S	Group R 0.5	Group R 1.0	P value
Number of patients	25	25	25	
Sex (male/female)	12/13	12/13	13/12	0.95
Age (years)	43.24 ± 12.32	46.80 ± 10.53	41.76 ± 11.64	1.27
Height (cm)	164.56 ± 6.66	164.32 ± 10.01	167.18 ± 9.46	0.45
Weight (kg)	66.66 ± 10.61	64.43 ± 12.43	65.72 ± 10.97	0.24
BMI (kg/m^2)	24.54 ± 3.00	23.67 ± 2.55	23.47 ± 3.07)	0.97

Data are presented as mean ± standard deviation or *n* patients.
Group S, saline infusion group; Group R 0.5, remifentanil 0.5 μg/kg/minute infusion group; Group R 1.0, remifentanil 1.0 μg/kg/minute infusion group; F, female; M, male; BMI, body mass index.

Table 2. Onset times to reach TOFR of 25% and TOF of 0 in the three study groups

	Group S (n = 25)	Group R 0.5 (n = 25)	Group R 1.0 (n = 25)	P value
TOF 0 (s)	130.0 ± 6.4	142.6 ± 6.0*	183.0 ± 11.6*,†	<0.001
TOFR 25% (s)	96.5 ± 6.4	106.9 ± 7.2*	147.2 ± 11.3*,†	<0.001

Data are presented as mean ± standard deviation.
TOF, train-of-four; TOFR, TOF ratio; Group S, saline infusion group; Group R 0.5, remifentanil 0.5 μg/kg/minute infusion group; Group R 1.0, remifentanil 1.0 μg/kg/minute infusion group.
(*$P < 0.05$ vs. Group R 0.5, †$P < 0.05$ vs. Group S.)

revealed significant differences among the groups ($P < 0.05$). The hemodynamic changes over time demonstrated significantly lower MBP and HR. MBP and HR were calculated with respect to their difference between baseline and T_0. The mean values and standard deviations were also calculated. Comparison of these values revealed statistically significant differences ($P < 0.05$) (Table 3).

The BP and HR markedly decreased during intubation in the groups with remifentanil infusion.

Discussion

The premise of this study is that continuous infusion of remifentanil influences the time to reach optimal neuromuscular blockade for tracheal intubation using rocuronium under TOF monitoring. The study results indicate that an increased remifentanil dose delays the onset time to reach optimal neuromuscular blockade.

Remifentanil has an ester bond that is quickly hydrolyzed in plasma and tissue; therefore, the onset time and duration of action of remifentanil are short.[11,12] Remifentanil is commonly used to maintain hemodynamic stability during tracheal intubation and is considered to provide an optimal pharmacological profile to treat the potentially adverse hemodynamic responses of tracheal intubation.[13] However, the adverse effects of remifentanil are similar to those of other opioids and include intense vagotonic and sympatholytic effects that result in bradycardia, hypotension, chest wall rigidity, nausea, and vomiting.[12,14] Several studies have shown that remifentanil

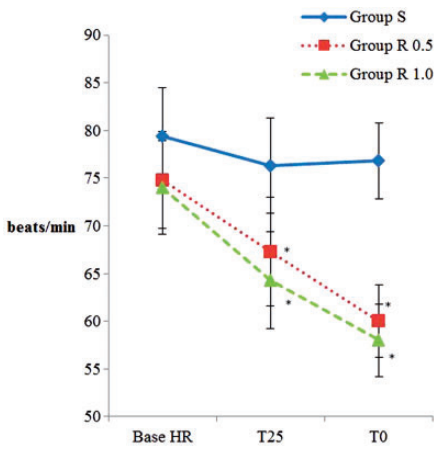

Figure 1. Comparison of the heart rate among the saline infusion group (Group S), remifentanil 0.5 μg/kg/minute infusion group (Group R 0.5), and remifentanil 1.0 μg/kg/minute infusion group (Group R 1.0).
HR, heart rate; Base, baseline; T25, train-of-four ratio 25%; T0, train-of-four 0. *$P < 0.05$ vs. baseline in the same group using two-way repeated-measures analysis of variance.

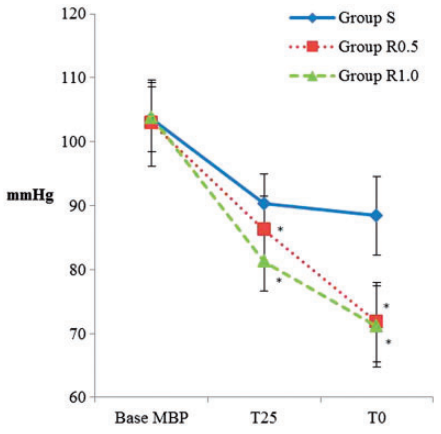

Figure 2. Comparison of the mean blood pressure among the saline infusion group (Group S), remifentanil 0.5 μg/kg/minute infusion group (Group R 0.5), and remifentanil 1.0 μg/kg/minute infusion group (Group R 1.0).
MBP, mean blood pressure; Base, baseline; T25, train-of-four ratio 25%; T0; train-of-four 0.
*$P < 0.05$ vs. baseline in the same group using two-way repeated-measures analysis of variance.

causes cardiovascular compromise during induction, which in turn alleviates the sympathetic stimulation caused by endotracheal intubation.[15] These studies proved that remifentanil decreases the systemic circulation. Therefore, continuous infusion of remifentanil at different doses affects neuromuscular pharmacodynamics.

Rocuronium bromide is a widely used neuromuscular relaxant. Its onset and duration are affected by various inhalation anesthetics, local anesthetics, and adjuvant drugs such as esmolol and ephedrine.[6,7,16] The delayed onset time of rocuronium is probably due to decreased cardiac output, circulation time, and muscle perfusion. Kuipers et al.[17] reported that cardiac output influences rocuronium pharmacokinetics and pharmacodynamics.

When using remifentanil, cardiac output can decrease and the onset time of rocuronium can be affected. We can therefore assume that an increased remifentanil dose can delay the time to reach optimal blockade for intubation. The TOFR was used to determine the accurate optimal onset time in the present study.

A significant increase in the proper induction time was proven with TOF monitoring during infusion with remifentanil at 1.0 μg/kg/minute. This study revealed significant differences among the three groups. The BP and HR decreased more from baseline to T_0 in the groups with continuous infusion of remifentanil than in the saline group. All patients enrolled in the study had an ASA physical status of I or II, implying that they would respond well to the hemodynamic changes induced by endotracheal intubation. In patients with cardiovascular problems, however, the changes in BP and HR measured in this study could have significant consequences.

Our study has one main limitation. A previous study showed that remifentanil must be administered after rocuronium to decrease the risk of adverse effects. This is

Table 3. Difference in MBP and HR between baseline and train-of-four of 0 among the three study groups

	Group S (n = 25)	Group R 0.5 (n = 25)	Group R 1.0 (n = 25)	P value
Differential MBP	13.04 ± 9.22	22.44 ± 8.98*	34.32 ± 12.78*,†	<0.05
Differential HR	2.56 ± 8.42	14.84 ± 7.53*	16.00 ± 6.06*,†	<0.05

Data are presented as mean ± standard deviation.
Group S, saline infusion group; Group R 0.5, remifentanil 0.5 μg/kg/minute infusion group; Group R 1.0, remifentanil 1.0 μg/kg/minute infusion group; MBP, mean blood pressure; HR, heart rate.
(*$P < 0.05$ vs. Group R 0.5, †$P < 0.05$ vs. Group S.)

because the target effect–site concentration of remifentanil has shorter latency than rocuronium.[18] For rapid-sequence induction, remifentanil relieves the surge of sympathetic tone after endotracheal intubation. In conclusion, continuous infusion of remifentanil increases the optimal neuromuscular blockade time for tracheal intubation.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Thomson IR. The haemodynamic response to intubation: a perspective. *Can J Anaesth* 1989; 36: 367–369.
2. Roy WL, Edelist G and Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979; 51: 393–397.
3. Kovac AL. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. *J Clin Anesth* 1996; 8: 63–79.
4. Park SJ, Shim YH, Yoo JH, et al. Low-dose remifentanil to modify hemodynamic responses to tracheal intubation: comparison in normotensive and untreated/treated hypertensive Korean patients. *Korean J Anesthesiol* 2012; 62: 135–141.
5. Schlaich N, Mertzlufft F, Soltesz S, et al. Remifentanil and propofol without muscle relaxants or with different doses of rocuronium for tracheal intubation in outpatient anaesthesia. *Acta Anaesthesiol Scand* 2000; 44: 720–726.
6. Ozcan A, Ozcan N, Gulec H, et al. Comparison of the effects of fentanyl, remifentanil, and dexmedetomidine on neuromuscular blockade. *J Anesth* 2012; 26: 196–199.
7. Szmuk P, Ezri T, Chelly JE, et al. The onset time of rocuronium is slowed by esmolol and accelerated by ephedrine. *Anesth Analg* 2000; 90: 1217–1219.
8. Hyun D, Ryu HB and Kim MW. Effect of isoflurane versus propofol-remifentanil anesthesia on neuromuscular blockade and hemodynamic responses by cisatracurium bolus injection. *Korean J Anesthesiol* 2011; 61: 297–301.
9. Fuchs-Buder T, Claudius C, Skovgaard LT, et al. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand* 2007; 51: 789–808.
10. Foldes FF, Nagashima H, Nguyen HD, et al. The neuromuscular effects of ORG9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; 75: 191–196.
11. Glass PS, Hardman D, Kamiyama Y, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesth Analg* 1993; 77: 1031–1040.
12. Beers R and Camporesi E. Remifentanil update: clinical science and utility. *CNS Drugs* 2004; 18: 1085–1104.

13. Thompson JP, Hall AP, Russell J, et al. Effect of remifentanil on the haemodynamic response to orotracheal intubation. *Br J Anaesth* 1998; 80: 467–469.
14. Dahaba AA. Remifentanil pharmacokinetics. *Anesth Analg* 2002; 94: 1674.
15. Yoon SH, Kim KH and Seo SH. Dose of remifentanil for minimizing the cardiovascular changes to tracheal intubation in pediatric patients. *Korean J Anesthesiol* 2010; 59: 167–172.
16. Norman E, Wikstrom S, Hellstrom-Westas L, et al. Rapid sequence induction is superior to morphine for intubation of preterm infants: a randomized controlled trial. *J Pediatr* 2011; 159: 893–9.e1.
17. Kuipers JA, Boer F, Olofsen E, et al. Recirculatory pharmacokinetics and pharmacodynamics of rocuronium in patients: the influence of cardiac output. *Anesthesiology* 2001; 94: 47–55.
18. Na HS, Hwang JW, Park SH, et al. Drug-administration sequence of target-controlled propofol and remifentanil influences the onset of rocuronium. A double-blind, randomized trial. *Acta Anaesthesiol Scand* 2012; 56: 558–564.