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ORIGINAL ARTICLE

Effectiveness of the timing principle with high-dose rocuronium during rapid sequence induction with lidocaine, remifentanil and propofol

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Abstract
Purpose The main purpose of this study was to examine the effectiveness of the timing principle with 1 mg kg^{-1} rocuronium for rapid sequence intubation. As secondary outcomes, propofol and lidocaine with or without remifentanil were examined to note their effects on the cardiovascular responses to laryngoscopy and intubation.
Methods Thirty patients were randomly allocated to one of two groups of 15 patients each: a lidocaine-treated group (L) and a lidocaine/remifentanil-treated group (LR). Thirty seconds after lidocaine 1 mg kg^{-1} with or without infusion of remifentanil 1 μg kg^{-1} min^{-1}, all patients received a bolus of rocuronium 1 mg kg^{-1}. Shortly afterwards, patients were given propofol 2–2.5 mg kg^{-1}. Intubating conditions and cardiovascular responses were observed 60 s after rocuronium. The time to spontaneous recovery of visible train-of-four (TOF) counts of 4 was observed at the thumb during 1.0–1.5% end-tidal sevoflurane and remifentanil anesthesia.
Results All patients had excellent or good intubating conditions. Hypertension and tachycardia during laryngoscopy were well prevented in group LR, whereas they were significantly observed in group L. The times to reappearance of TOF counts of 4 were comparable in all groups [mean (SD); 63.6 (8.6) min in group L and 63.5 (11.6) min in group LR].
Conclusion Application of the timing principle with 1 mg kg^{-1} rocuronium is beneficial for rapid tracheal intubation. Co-administered lidocaine, remifentanil and propofol can definitely suppress cardiovascular responses during laryngoscopy and intubation.

Keywords Rapid-sequence intubation · Timing principle · Rocuronium

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Introduction

The procedure termed "the timing principle" [1, 2] involves administering an intubating dose of neuromuscular blocking agent prior to inducing general anesthesia, and it enables the interval from the patient's loss of consciousness following hypnotics to tracheal intubation to be considerably shortened. Many anesthetics can reduce lower and upper esophageal sphincter tone and tend to promote gastroesophageal regurgitation into the pharynx [3]. Particularly in an emergent patient with a full stomach, the incidence of pulmonary aspiration during induction of general anesthesia will be 3–4 times higher than that for patients undergoing proposed elective surgery [4]. It is highly likely that the timing principle can decrease the risk of pulmonary aspiration. As might be expected, rocuronium, with its more rapid onset of action, is superior to vecuronium and atracurium for rapid-sequence intubation. The study reported by Nelson and colleagues [5] showed that a relatively low dose of rocuronium of 0.6 mg kg^{-1} given 20 s prior to thiopental provided excellent or good intubating conditions that were equivalent to those afforded by suxamethonium 1 mg kg^{-1} for rapid-sequence induction. Although these previous studies [5, 6] only examined the timing principle with 0.6 mg kg^{-1} rocuronium, it may be easier to improve intubating conditions within a shorter time period when using a higher dose of rocuronium. Therefore, the main purpose of this study

was to examine the effectiveness of the timing principle with 1 mg kg^{-1} rocuronium for rapid-sequence intubation. Furthermore, it is important to deepen anesthesia to prevent cardiovascular responses during rapid-sequence induction using the timing principle. Therefore, combinations of lidocaine and propofol with or without remifentanil for inhibiting hypertensive response during laryngoscopy were compared.

Materials and methods

After the protocol had been approved by the Hospital Ethics Committee on Human Rights in Research, 30 adult patients (males: 14, females: 16) consented to participate in this study. Patients were ASA physical status I or II, 20–60 years of age, and were undergoing elective surgery. None of the patients had a difficult airway, a previous history of hypertension, neuromuscular, hepatic and renal disorders, or were taking any drugs that were known to interact with neuromuscular blocking agents. Patients with BMIs of $\geq$25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg the night before and on the morning of the surgery, and i.m. midazolam 0.03–0.04 mg kg^{-1}. On arrival at the operating room, all patients were monitored for ECG, non-invasive blood pressure and pulse oximetry. An i.v. infusion of acetated Ringer's solution 8–10 ml kg^{-1} h^{-1} was started via a cannula in the right forearm. Patients were randomly allocated via computer-generated randomization to one of two groups (each containing 15 patients) in a double-blind manner. One group was treated with a bolus of 1 mg kg^{-1} lidocaine (L), while the other received a bolus of lidocaine and continuous infusion of remifentanil at a rate of 1 μg kg^{-1} min^{-1} (LR). Patients received 100% oxygen for 2 min through an anesthesia facemask. Thirty seconds after intravenous administration of lidocaine with or without continuous infusion of remifentanil, all of the patients received a bolus of rocuronium 1 mg kg^{-1} while awake, and they graded the pain felt upon injection with rocuronium using a four-point scale (none, mild, moderate and severe). Shortly afterwards, the patients were given propofol 2–2.5 mg kg^{-1} over 20 s, and loss of consciousness was judged by loss of eyelash reflex and response upon calling out the patient's name. Concurrently, the bispectral index value was confirmed to be 60 or below (BIS monitor A-2000 Aspect Medical Systems, Norwood, MA, USA). Sixty seconds after the administration of rocuronium, the patient's trachea was intubated with a 8.0 mm ID endotracheal tube (in males) or a 7.0 mm ID tube (in females) by a staff anesthesiologist who was blinded to the grouping and finally entered the room during propofol injection. At this point, the intubating conditions were graded as either excellent, good or poor, as described in the guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents [7]. The patient's blood pressure and heart rate were recorded before induction of anesthesia and immediately after tracheal intubation. Anesthesia was maintained with 1.0–1.5% end-tidal sevoflurane and remifentanil 0.2–0.25 μg kg^{-1} min^{-1}. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R (Nihon Kohden, Tokyo, Japan). The patient's rectal temperature was monitored using Mon-a-Therm (Mallinckrodt, Anesthesia Products Inc., St. Louis, MO, USA) and maintained at >36°C using a warming mattress, a blanket (Thermacare and Medi-Therm II, Gaymer Industries, NY, USA), and warmed i.v. fluids. The ulnar nerve was stimulated at the wrist with a train-of-four (TOF) mode delivered at 2 Hz every 12 s (Innervator NS-252, Fisher & Paykel, Auckland, New Zealand), and movement of the ipsilateral thumb was visually assessed by the same staff anesthesiologist. The output current was kept at 40–50 mA. The time to spontaneous recovery of visible TOF counts of 4 was recorded. All patients were interviewed the day after the operation and specifically asked about any weakness felt before anesthesia was induced and unpleasant memories of the laryngoscopy tracheal intubation.

Calculation of sample size was based on preliminary data for an averaged intubating score (8.6 ± 0.8) 60 s after 1 mg kg^{-1} rocuronium. A power analysis suggested that a sample size of 15 patients in each group should be adequate to detect a 10% difference in the intubating score with a two-sided significance level α of 0.05 and a power of 0.8. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). The paired Student's t test or Wilcoxon rank sum test was used as appropriate for group comparisons. A P value of <0.05 was considered statistically significant.

Results

Patient characteristics did not differ between the two groups (Table 1). Tracheal intubation was successful within 20 s in all patients. All patients had excellent intubating conditions, with two exceptions where the intubating conditions were good in the group L. Hypertension and tachycardia during laryngoscopy were well prevented in group LR, whereas they were significantly observed in group L. Immediately after intubation, mean arterial pressure and heart rate in group L increased by 43 and 42% of the baseline values, respectively (Table 2). Severe pain upon injection with rocuronium was not seen in either

Table 1 Patient characteristics

	Lidocaine-treated group	Lidocaine/remifentanil-treated group
Gender (M:F)	7:8	7:8
Age (years)	42.4 (16.0)	42.8 (15.4)
Weight (kg)	57.8 (10.3)	56.6 (8.7)
Height (cm)	164.8 (7.4)	165.8 (7.8)

Data are presented as mean (SD). No significant differences were seen among the groups

Table 2 Cardiovascular responses during laryngoscopy

	Mean blood pressure		Heart rate	
	Pre	Post	Pre	Post
Lidocaine-treated group	84.6 (9.3)	120.1 (8.4)[#]	72.5 (10.1)	101.5 (14.1)[#]
Lidocaine/remifentanil-treated group	84.9 (11.1)	85.8 (11.1)	82.7 (18.4)	80.7 (16.5)

Data are presented as number of patients. "Pre" and "post" mean the periods before and after laryngoscopy and tracheal intubation

[#] Statistically significant differences ($P < 0.05$) were seen when comparing factors between the periods before and after laryngoscopy

Table 3 Graded severity of pain on injection of rocuronium

	None	Mild	Moderate	Severe
Lidocaine-treated group	4	8	3	0
Lidocaine/remifentanil-treated group	3	10	2	0

Data are presented as number of patients. No statistically significant difference was seen between the groups

group (Table 3). The times to reappearance of TOF counts of 4 were comparable between the groups [63.6 (8.6) min in group L and 63.5 (11.6) min in group RL]. In the postoperative interview, none of the patients complained that they had felt weakness before anesthesia was induced with propofol, or that they remembered having been intubated tracheally.

Discussion

The ultimate objective for rapid-sequence induction is to attain optimum intubating conditions rapidly and reliably without side effects. The present study showed that the use of the timing principle with the combined administration of rocuronium 1.0 mg kg^{-1} with lidocaine, remifentanil and propofol during the induction of general anesthesia definitely enabled tracheal intubation 60 s after rocuronium without any onset of untoward weakness, unpleasant patient memories and sympathomimetic effects during laryngoscopy.

In the present study, the optimal dose of rocuronium for providing excellent intubating conditions within 60 s during rapid-sequence induction was found to be 1 mg kg^{-1}. The dose regimen was planned based on the results obtained in previous studies [8, 9]. The dose of rocuronium needed for a 95% probability of successful intubation within 60 s was found to be 1.04 mg kg^{-1} during induction with fentanyl and propofol [8]. Additionally, the incidence of clinically acceptable intubating conditions 60 s after rocuronium 1.0 mg kg^{-1} was given along with propofol was 93.2% [9]. It was therefore found that rocuronium 1.0 mg kg^{-1} can provide intubating conditions that are equivalent to rapid-sequence intubation with suxamethonium. In this study, all of the patients had excellent or good intubating conditions. Thus, it was confirmed that an intubating dose of 1.0 mg kg^{-1} rocuronium was appropriate for rapid-sequence intubation using the timing principle. The anesthetics used during rapid-sequence induction may also help to ease tracheal intubation. Administration of i.v. lidocaine has been shown to suppress the cough reflex after the insertion of a tracheal tube [10]. Propofol has a greater depressant effect on jaw tone, laryngeal and pharyngeal reflex than thiopentone [11, 12]. Similarly, remifentanil suppresses jaw tone and airway reflex, and its combination with propofol for induction has been shown to provide adequate conditions for laryngoscopy and intubation without the need for concomitant muscle relaxants [13]. Apneic and analgesic effects of remifentanil may help to improve intubating conditions [14]. It is therefore possible that the combination of lidocaine, remifentanil and propofol may have a synergistic effect on the intubating conditions provided by rocuronium-induced neuromuscular block.

An increase in the dose of rocuronium is associated with an increase in the recovery time. The average duration of action from the administration of rocuronium 1.0 mg kg^{-1} to the reappearance of TOF counts of 4 was approximately 64 min for 1.0–1.5% sevoflurane and remifentanil anesthesia in this study. The visual reappearance of TOF counts of 4 means that the recovery of twitch tension has already reached >25% of that of the control [15], and this would have been promptly facilitated by neostigmine [16]. When anesthetized intravenously with propofol and opioid, the clinical duration of action of rocuronium 1.0 mg kg^{-1} is shortened to about 50 min [17]. It is therefore suggested that the timing principle with rocuronium 1.0 mg kg^{-1} could be applied for an anticipated length of surgery of around 60 min, unless contraindications to anticholinesterases are present.

The timing principle with slower-onset vecuronium [1] and atracurium [2] was first introduced in clinical

anesthesia as a method of rapid-sequence intubation. To ensure an effective timing principle, general anesthesia should be induced when the patient feels the onset of clinical weakness. Therefore, the timing principle may not be appropriate for patients who cannot cooperate and understand this procedure. In addition, weakness such as ptosis, difficulty in swallowing and inability to take deep breaths following an intubating dose of neuromuscular blocking agent can make patients uncomfortable and agitated. The timing principle with rapid-onset rocuronium, on the other hand, enables the induction of general anesthesia shortly after an injection of rocuronium without the need to observe the patient's reaction. When higher-dose rocuronium is administered, the lag before detectable twitch depression is shortened to only about 30 s [18]. It is therefore recommended that hypnotic drugs should be injected 15–20 s after the administration of rocuronium, as done in the present study, to prevent patient discomfort. The validity of this anesthetic timing is supported by the results of the postoperative interviews, where no patients reported feeling weakness and agitation before the induction of anesthesia with propofol. Furthermore, the effective prevention of pain upon the injection of rocuronium should be considered in relation to the timing principle. In a preliminary study, severe pain upon the injection of rocuronium was seen in 86.7% of patients without lidocaine. Pretreatment with i.v. lidocaine is the preferred way to resolve this problem [19].

The effectiveness of lidocaine at blunting the hemodynamic response to endotracheal intubation has been reported in the literature [20, 21], whereas our study could not show the solitary effect of lidocaine. The best dose of intravenous lidocaine for attenuating cardiovascular responses to laryngoscopy and intubation has been established to be 1.5 mg kg^{-1} [20]. Moreover, the timing of lidocaine injection could be important. It was shown that lidocaine has a beneficial effect on hemodynamic stability when administered 3 min before laryngoscopy [21]. Therefore, the utilization of different dosing regimens must be the reason for an inability to blunt pressor responses. By contrast, undesirable hemodynamic effects such as hypertension and tachycardia were well prevented in group LR. Remifentanil reduces cardiovascular changes induced by nociceptive stimuli dose dependently. The effect-site concentration of remifentanil that blunted cardiovascular responses to tracheal intubation in 95% of patients was 6.0 ng ml^{-1} [22]. In this study, remifentanil was infused at a rate of 1 μg kg^{-1} min^{-1} for 90 s before laryngoscopy. In the meantime, the effect-site concentration of remifentanil was predicted to rise to only 4.1 ng ml^{-1} by a computerized pharmacokinetic model. As seen in the LR group, it is therefore likely that remifentanil combined with lidocaine and propofol could synergistically prevent hypertension and tachycardia associated with laryngoscopy and tracheal intubation.

In conclusion, the application of the timing principle with 1.0 mg kg^{-1} rocuronium and lidocaine 1 mg kg^{-1} definitely enabled rapid-sequence intubation in 60 s. The combination of remifentanil with lidocaine and propofol exhibited a synergism that inhibited hypertension and tachycardia caused by laryngoscopy and tracheal intubation.

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References

1. Culling RD, Middaugh RE, Menk EJ. Rapid tracheal intubation with vecuronium: the timing principle. J Clin Anesth. 1989; 1:422–5.
2. Koh KF, Chen FG. Rapid tracheal intubation with atracurium: the timing principle. Can J Anaesth. 1994;41:688–93.
3. Ng A, Smith G. Gastroesophageal reflux and aspiration of gastric contents in anesthetic practice. Anesth Analg. 2001;93:494–513.
4. Janda M, Scheeren TWL, Nöldge-Schomburg GFE. Management of pulmonary aspiration. Best Pract Res Clin Anaesthesiol. 2006;20:409–27.
5. Nelson JM, Morell RC, Butterworth IVJF. Rocuronium versus succinylcholine for rapid-sequence induction using a variation of the timing principle. J Clin Anesth. 1997;9:317–20.
6. Sieber TJ, Zbinden AM, Curatolo M, Shorten GD. Tracheal intubation with rocuronium using the "timing principle". Anesth Analg. 1998;86:1137–40.
7. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand. 2007;51:789–808.
8. Kirkegaard-Nielsen H, Caldwell JE, Berry PD. Rapid tracheal intubation with rocuronium. A probability approach to determining dose. Anesthesiology. 1999;91:131–6.
9. Andrews JI, Kumar N, van den Brom RHG, Olkkola KT, Roest GJ, Wright PMC. A large simple randomized trial of rocuronium versus succinylcholine in rapid–sequence induction of anaesthesia along with propofol. Acta Anaesthesiol Scand. 1999;43:4–8.
10. Davidson JAH, Gillespie JA. Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine. Br J Anaesth. 1993;70:163–6.
11. McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. Anaesthesia. 1988; 43:638–40.
12. Barker P, Langton JA, Wilson IG, Smith G. Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol. Br J Anaesth. 1992;69:23–5.
13. Park HJ, Lee JR, Kim CS, Kim SD, Kim HS. Remifentanil halves the EC50 of propofol for successful insertion of the laryngeal mask airway and laryngeal tube in pediatric patients. Anesth Analg. 2007;105:57–61.
14. Yazicioglu H, Muslu S, Yamak B, Erdemli O. Laryngeal mask airway insertion with remifentanil. Acta Anaesthesiol Belg. 2005;56:171–6.
15. O'hara DA, Fragen RJ, Shanks CA. Comparison of visual and measured train-of-four recovery after vecuronium-induced neuromuscular blockade using two anaesthetic techniques. Br J Anaesth. 1986;58:1300–2.

16. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Anesth Analg. 2004;99:1080–5.
17. Lowry DW, Mirakhur RK, McCarthy GJ, Carroll MT, McCourt KC. Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. Anesth Analg. 1998; 87:936–40.
18. Suzuki T, Mizutani H, Miyake E, Fukano N, Saeki S, Ogawa S. Infusion requirements and reversibility of rocuronium at the corrugator supercilii and adductor pollicis muscles. Acta Anaesthesiol Scand. 2009;53:1336–40.
19. Turan A, Memiş D, Karamanlioğlu B, Süt N, Pamukçu Z. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. Anaesth Intensive Care. 2003;31:277–81.
20. Abou-Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. Can Anaesth Soc J. 1977; 24:12–9.
21. Tam S, Chung F, Campbell M. Intravenous lidocaine: optimal time of injection before tracheal intubation. Anesth Analg. 1987;66:1036–8.
22. Albertin A, Casati A, Federica L, Roberto V, Travaglini V, Bergonzi P, Torri G. The effect-site concentration of remifentanil blunting cardiovascular responses to tracheal intubation and skin incision during bispectral index-guided propofol anesthesia. Anesth Analg. 2005;101:125–30.