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ORIGINAL ARTICLE

The effects of nicardipine or esmolol on the onset time of rocuronium and intubation conditions during rapid sequence induction: a randomized double-blind trial

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Abstract
Purpose The main aims of rapid sequence induction (RSI) are prompt and adequate muscle relaxation for tracheal intubation and hemodynamic stability during and after intubation. The purpose of the present study was to investigate the effects of nicardipine and esmolol on the action of rocuronium and intubation conditions during RSI.
Methods Adult patients ($n = 82$) were randomly allocated to one of three groups. One minute prior to the induction of sevoflurane-based general anesthesia, patients received 20 μg/kg of nicardipine (N group; $n = 27$) or 0.5 mg/kg of esmolol (E group; $n = 27$), or 5 ml of saline (C group; $n = 28$). Patients were assessed according to intubation conditions, the onset time of rocuronium, mean arterial pressure (MAP), and heart rate (HR) during RSI.
Results The intubation conditions and score were significantly better in the C and N groups than in the E group ($P < 0.001$). The onset time of rocuronium was shortened in the N group and prolonged in the E group when compared to the C group ($P < 0.001$). A significant attenuation in the increase of MAP immediately after intubation was observed in the N group as compared with the C and E groups ($P < 0.008$). HR was significantly lower in the E group than in the N and C groups ($P < 0.01$).
Conclusion Pretreatment with nicardipine for RSI improved intubation conditions and shortened the onset time of rocuronium and attenuated changes in MAP after intubation. Esmolol may disturb intubation conditions and the onset of action of rocuronium, despite being effective in alleviating responses of HR after RSI.

Keywords Esmolol · Nicardipine · Rapid sequence induction

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Introduction

Rapid sequence induction (RSI) is required for various conditions that pose a risk of aspiration, such as a full stomach, an intestinal obstruction, a history of an esophageal reflux, and cesarean section [1]. The main aim of RSI is to minimize the interval between the loss of protective airway reflexes and tracheal intubation. Because the airway is unprotected during this critical period, the patient becomes vulnerable to aspiration of their gastric contents. Inadequate neuromuscular blockade during RSI may cause failure of the vocal cords to open fully, and poor intubation conditions, which can lead to vocal cord damage, postoperative hoarseness, and failure of endotracheal intubation [2]. The ideal muscle relaxant for RSI must therefore have a rapid onset of action. Rocuronium has become an alternative for patients who cannot receive succinylcholine, because it is known to have the most rapid onset among nondepolarizing muscle relaxants. The speed of onset of rocuronium may depend in part on dosage, co-administered drugs, and physiologic factors such as cardiac output, circulation time, and muscle perfusion [3].

Additional important considerations during RSI include severe hemodynamic changes, including hypertension or aggravated tachycardia in response to sympathetic stimulation by tracheal intubation. This often results from insufficient or omitted mask ventilation, especially during general anesthesia using volatile anesthetics [4]. Nicardipine and

esmolol are considered appropriate for the control of hemodynamics during RSI due to their rapid onset and short duration. However, there have been no reports determining if these drugs influence intubation conditions and the action of rocuronium. We investigated the effects of nicardipine and esmolol on the action of rocuronium, intubation conditions, and cardiovascular responses during RSI in this double-blind randomized study.

Methods

The study was approved by the institutional review board (approval number: K-1401-001-002)) and registered in the national clinical trial (http://cris.nih.go.kr. Ref: KCT 0001177). After obtaining informed consents, patients aged 20–65 years with physical status 1 or 2, according to the American Society of Anesthesiologists were included in this study. Each patient was scheduled to undergo elective general surgery, such as open thyroid surgery, endoscopic thyroidectomy, or orthopedic surgery. The exclusion criteria included conditions that pose a risk of difficult endotracheal intubation, including a body mass index (BMI) >30 kg/m^2 or <16.5 kg/m^2, chronic preoperative β-adrenergic blocker treatment, a history of hypertension, neuromuscular disease, or renal disease. Eligible patients were randomly allocated into one of the three groups using the sealed envelope method—pretreatment with 20 μg/kg of nicardipine (N group), 0.5 mg/kg of esmolol (E group), and 5 ml of isotonic saline (C group).

For pre-medications, midazolam and glycopyrrolate were administered at doses of 0.05 mg/kg and 0.2 mg, respectively. They were administered intramuscularly 30 min prior to the patient entering the operating room. Prior to anesthetic induction, the mean arterial pressure (MAP), BIS (bispectral index), and heart rate (HR) were recorded with the patient in a stable condition. All the drugs used in this study (nicardipine, esmolol, and isotonic saline) were prepared by a nurse who did not participate in this study, and drug preparation was performed under supervision by an investigator. To maintain blinding during the study, nicardipine and esmolol were diluted in isotonic saline to a total volume of 5 ml. The pretreatment drugs were administered 60 s prior to the induction of anesthesia by an anesthesiologist, who was blind to the patient's group assignment. Induction, endotracheal intubation, and several evaluations related to our study were performed by the same anesthesiologist. After adequate preoxygenation, anesthesia was induced with 5 mg/kg of thiopental. Following loss of consciousness, 1 mg/kg of lidocaine was administered and mask ventilation was performed with sevoflurane at 5 vol%, and O_2 at 6 L/min. Muscle relaxation was monitored using a train-of-four (TOF) Watch® SX (Oregon Ireland Limited, Swords, Dublin, Ireland) and assessed through measurement of the TOF response of the adductor pollicis. Cutaneous electrodes were placed over the flexor carpi ulnaris tendon to stimulate the ulnar nerve of the arm receiving the intravenous catheter, but without the blood pressure monitor cuff. The fingers (except thumb) and the forearm were fixed to a rigid plate using an adhesive bandage to prevent errors resulting from artifacts. The reference point was verified through the calibration function of the nerve stimulator before the injection of 1 mg/kg of rocuronium. The temperature of the palm skin was maintained >32 °C. Supramaximal square wave impulses spanning 0.2 s in duration were administered at 2 Hz every 15 s until no response was detected. The onset time of rocuronium was defined as the time from the end of the administration to the disappearance of all four twitches in the TOF response.

Following the injection of rocuronium, rocuronium-induced withdrawal movement was observed by the blinded anesthesiologist. Withdrawal movement was graded by the investigator according to the following scale—1 = no response, 2 = movement at wrist only, 3 = movement/withdrawal involving arm only (elbow/shoulder), and 4 = generalized response (movement/withdrawal in more than one extremity, cough, or breath holding) [5].

Tracheal intubation was performed 60 s after the administration of rocuronium. During the tracheal intubation procedure, a laryngoscopic review was conducted according to the classification proposed by Cormack and Lehane [6]. We evaluated the intubation conditions using a scoring system that yields both a numerical and qualitative intubation score, as prescribed by studies of neuromuscular blocking drugs to ensure good clinical research practice [7]. The numerical intubation score was obtained by summing the scores assigned to the factors—laryngoscopy, vocal cords and response to intubation (individually rated with a score from 1 = worst to 3 = best). The qualitative intubation scores were defined as excellent (all three factors received a score of 3), good (all three factors received a score of 3 or 2), and poor (at least one factor received a score of 1). Excellent and good intubation conditions were considered clinically acceptable while poor intubation conditions were considered clinically unacceptable. Following endotracheal intubation, anesthesia was maintained with O_2 at 2 L/min, N_2O at 2 L/min, and sevoflurane at 1–2 vol% for a BIS of 40–60. The MAP and HR were measured prior to administration of the test drug (B), immediately after intubation (I), and 1, 2, 3, and 5 min thereafter (I1, I2, I3, I5). Any case in which the tracheal intubations were not completed within 60 s after the start of the intubation procedure was regarded as a failed case and excluded from the study.

If the systolic blood pressure was >160 mmHg, <80 mmHg, or HR was >110, <50 bpm, 1 min after intubation, then 0.5–1 mg of intravenous nicardipine, 2.5–5 mg of ephedrine, 5–10 mg of esmolol, or 0.1–0.2 mg of glycopyrrolate was

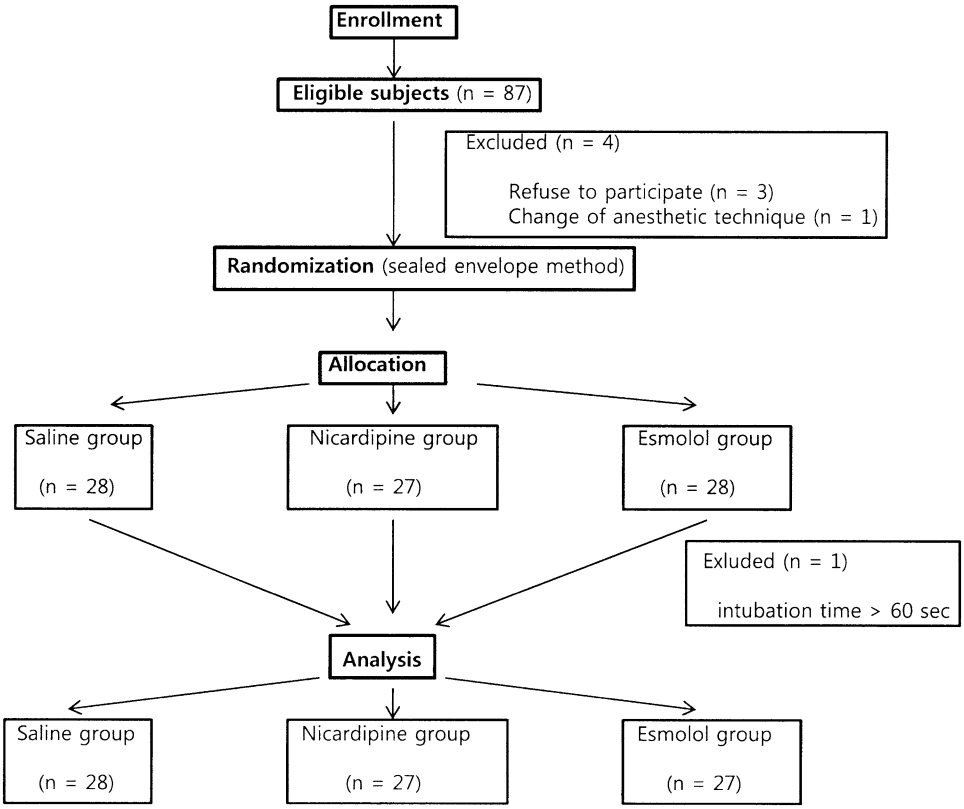

Fig. 1 Diagram depicting patient progression through enrollment

administered, respectively. The frequency of administration of additional nicardipine, esmolol, ephedrine, or glycopyrrolate was evaluated. Any adverse events relating to the pretreatment drugs and rocuronium were evaluated during induction of anesthesia. All patients were asked about any discomfort and unpleasant recall for the laryngoscopy and tracheal intubation the day after the operation. All patients were interviewed by a blinded investigator 24 h after surgery.

Statistical analysis

Based on a preliminary study, a power analysis indicated that 27 patients per group would be sufficient to detect a 25 % difference of the mean onset time between the groups, with a power >80 % at a significance level of 0.05. Data were reported as the means (standard deviation) or number (%), and the statistical significance analysis was performed using SPSS (Windows version 17.0, SPSS, IL, USA), and a P value <=0.05 was considered to indicate significance. Collected variables including age, body weight, height, intubation score, BIS, and onset time of rocuronium were compared using a one-way analysis of variance with a Bonferroni post hoc comparison. Differences in sex, ASA status, rocuronium-induced withdrawal response, laryngoscopic view, need of additional esmolol or nicardipine for hemodynamic stability and intubation conditions among the three groups were analyzed using the chi-squared test or Fisher's exact test. MAP and HR were analyzed using a repeated measures analysis of variance, and Turkey's test for post hoc analysis was performed to detect any significant differences among groups.

Results

Of the 87 patients that were enrolled, data from 82 patients were collected and analyzed. Figure 1 shows the progression of the patients through the experiment protocol. No significant differences were observed in the demographic data between the three groups (Table 1). All data were normally distributed. The incidence of withdrawal responses resulting from injection pain of rocuronium showed no significant difference among the groups.

All patients in the N and C groups demonstrated acceptable intubation conditions, while only 89 % of patients in the E group demonstrated acceptable intubation conditions; the remaining 11 % of patients in the E group demonstrated poor in intubation conditions ($P < 0.001$) (Table 2). The intubation score was higher in the N group ($P < 0.007$), and lower in the E group ($P < 0.001$) than in the C group. The onset time of rocuronium was significantly longer in the E group ($P < 0.003$) and shorter in the N group ($P < 0.001$) when compared to the C group. BIS values before induction, after intubation and laryngoscopic reviews were comparable among the groups ($P > 0.05$). The requirement for additional

Table 1 Patient demographics

	C group ($n = 28$)	N group ($n = 27$)	E group ($n = 27$)
Age (years)	48 (10)	38 (11)	41 (10)
Weight (kg)	61 (5)	58 (8)	57 (6)
Height (cm)	161 (7)	160 (7)	160 (6)
Female/male	24/4 (86/14)	20/7 (74/26)	23/4 (85/15)
ASA I/II	0/28 (0/100)	0/27 (0/100)	1/26 (4/96)
Withdrawal response (0/1/2)	17/9/2 (61/32/7)	18/9/0 (67/33/0)	18/9/0 (67/33/0)

Quantitative variables are displayed as mean (standard deviation) and the qualitative variables as frequency (percentages)

ASA American Society of Anesthesiologists physical status

esmolol or nicardipine was greater in the C group than in the E group ($P < 0.02$) and the N group ($P < 0.05$). There was a significant decrease of MAP in the N group than in the C group ($P < 0.001$) and the E group ($P < 0.007$) immediately after intubation, and in the C group at 1 min after intubation ($P < 0.006$) and at 2 min after intubation ($P < 0.039$) (Fig. 2). HR was significantly lower in the E group when compared with the C group ($P < 0.001$) and the N group ($P < 0.005$) immediately after intubation, and with the C group ($P < 0.001$) and the N group ($P < 0.005$) at 1 min after intubation (Fig. 3). Hypotension, bradycardia, and rescue treatments did not occur after intubation in any group.

In the postoperative interview, none of the patients complained of unpleasant memories from the intubation and the induction of anesthesia.

Discussion

RSI involves sufficient oxygenation, rapid injection of a series of drugs, and prompt intubation within 1 min of administering a neuromuscular blocking agent. Succinylcholine has been the mainstay of RSI for >50 years, primarily because of its rapid onset time. However, it is currently recognized as 'a pharmacologically dirty and dangerous drug' with potentially serious side-effects by some clinicians [8]. Rocuronium has become an alternative drug for RSI because it has a more rapid onset than most other neuromuscular blocking agents. The intubation conditions after the injection of 1 mg/kg of rocuronium were found to be acceptable (scoring either good or excellent) in 95 % of patients and were aligned with patients administered suxamethonium (97 %) [9]. In the present study, there were excellent intubation conditions for 85 % of patients in the N group and acceptable (excellent or good) intubation conditions for all patients in the N and C groups.

Some studies have established that, for various reasons, co-administered drugs may affect the onset of neuromuscular blockers [3, 10]. Ezri et al. [3] demonstrated that esmolol and ephedrine affected the onset time of rocuronium by altering the cardiac output (CO). Esmolol, a selective β1 blocker, possesses negative inotropic and chronotropic effects, thereby decreasing CO in both anesthetized healthy patients and those with left ventricular dysfunction [11]. The finding that esmolol delays the onset time of neuromuscular blockers is of special interest because esmolol is indicated and commonly used to improve hemodynamic stability both during RSI and during the conventional induction of anesthesia [12]. However, no evidence exists to suggest that esmolol disturbs the intubation conditions for RSI. We found unacceptable intubation conditions and delayed onset of rocuronium in the E group. Pretreatment using esmolol might reduce the advantage of rocuronium by delaying its action during RSI. Thus, it may be more reasonable to administer esmolol as late as possible following rocuronium injection in RSI to preserve the rapid-onset advantage of rocuronium.

Table 2 Intubation conditions

	C group ($n = 28$)	N group ($n = 27$)	E group ($n = 27$)
Intubation conditions			
Excellent/good	10/18 (36/64)	23/4 (85/15)	2/22 (7/82)
Acceptable (excellent + good)	28 (100)	27 (100)	24(89)
Poor	0 (0)	0 (0)	3 (11)*,†
Intubation score	8.3 (0.6)	8.9 (0.4)*,‡	7.6 (0.9)*,†
Onset of rocuronium (S)	112.1 (29)	80.6 (19)*,‡	136.7 (29)*,†
BIS			
Before induction	91 (2)	92 (3)	90 (3)
Just after intubation	51 (3)	49 (5)	51 (2)
C&L grade I/II	4/24 (14/86)	5/22 (18/82)	5/22 (18/82)
Additional esmolol	26 (93)‡	22 (82)	17 (63)
Additional nicardipine	3 (11)†,‡	0 (0)	0 (0)

Quantitative variables are displayed as mean (standard deviation) and the qualitative variables as frequency (percentages). *BIS* bispectral index, *C&L grade* Cormack and Lehane grade

* $P < 0.05$ vs C group.
† $P < 0.05$ vs N group.
‡ $P < 0.05$ vs E group

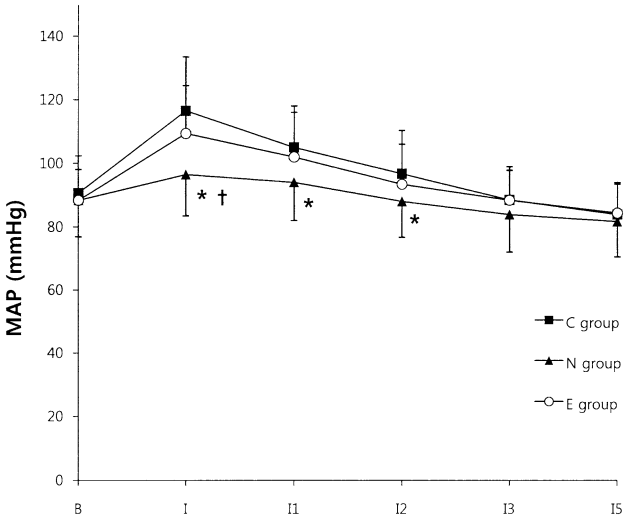

Fig. 2 Changes in mean arterial pressure (MAP). Values are mean ± SD *B* baseline, *I* immediately after intubation, *I1* 1 min after intubation, *I2* 2 min after intubation, *I3* 3 min after intubation, *I5* 5 min after intubation. **P* < 0.05 vs C group. †*P* < 0.05 vs E group

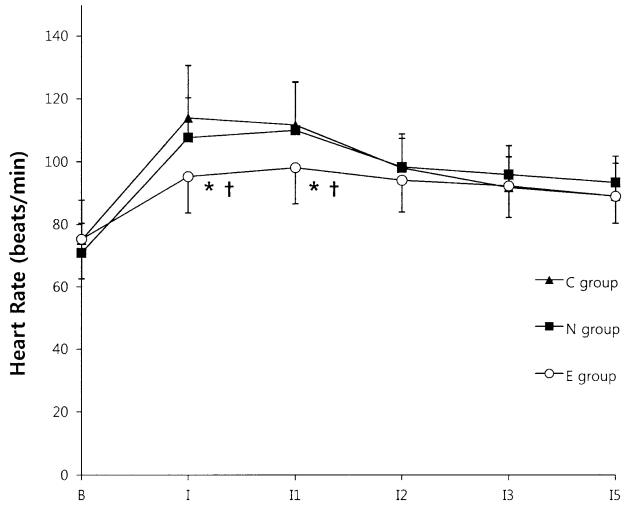

Fig. 3 Changes in heart rate (HR). Values are mean ± SD, *B* baseline, *I* immediately after intubation, *I1* 1 min after intubation, *I2* 2 min after intubation, *I3* 3 min after intubation, *I5* 5 min after intubation. **P* < 0.05 vs C group. †*P* < 0.05 vs N group

Nicardipine has been commonly used for hemodynamic stability during induction and intubation because of its rapid onset and short duration [13]. Takiguchi and Takaya [14] have shown a significant reduction in the vecuronium needed to maintain a steady neuromuscular blockade in patients given nicardipine intraoperatively. They suggested the potentiation of a neuromuscular blockade by calcium channel blockers. Yamada and Takino [10] demonstrated that the onset of vecuronium was shorter in patients who received nicardipine and that the duration of vecruonium was uninfluenced by nicardipine. It has been reported that calcium channel blockers may enhance neuromuscular block by acting mainly at the postjunctional region [15]. At present, there is no evidence pertaining to the effects of nicardipine on rocuronium-induced neuromuscular block. In this study, nicardipine shortened the onset time of rocuronium, which consequently played a role in improving intubation conditions for RSI. However, we could not demonstrate the mechanism of nicardipine-induced potentiation on the action of rocuronium, as characterized by increased CO, or calcium channel blockade. Little evidence exists in the literature to suggest that nicardipine may affect CO and muscle blood flow. Cheung et al. [16] demonstrated that nicardipine slightly increases global left ventricular systolic function without changing the left ventricular end-diastolic cavity area or CO. Lee et al. [17] have shown that nicardipine enhances paravertebral muscle blood flow (approximate mean 82.5 %) during controlled hypotension for spine surgery. However, isoflurane decreases this blood flow (ischemia; approximate mean 33.7 %) during controlled hypotension.

Hemodynamic changes during RSI may be potentiated more than in conventional induction because of the omission of mask ventilation and undelivered inhalational anesthetics. We found that most (93 %) patients allocated to the C group demonstrated a need for esmolol or nicardipine; therefore, it might be necessary to prevent or treat hemodynamic instability immediately after endotracheal intubation for RSI. Nicardipine effectively prevented hypertension but did not prevent the increase of HR, unlike esmolol, which was effective in attenuating changes of HR. Severe hypertensive episodes were not observed in the three groups because esmolol and nicardipine were administered immediately if HR and SBP increased after intubation. Rocuronium-induced injection pain or withdrawal movement is well known, and its incidence varies between 50 and 80 % [18, 19]. Rocuronium-induced injection pain may cause hemodynamic changes including hypertension and tachycardia and influence our results regarding hemodynamic changes occurring during RSI. Yavascaoglu et al. [20] have shown that esmolol, like lidocaine, reduces the frequency of pain and withdrawal reactions associated with rocuronium injection. In the present study, there were no differences in the rocuronium-induced withdrawal movement across the three groups following lidocaine injection, which has been commonly used for rocuronium-induced injection pain [21]. So et al. [22] revealed that when mixed with propofol to prevent injection pain, lidocaine did not affect the onset time of rocuronium, the resulting intubation conditions, and intubation-related hemodynamic changes.

We could not find any difference in the BIS between the three groups prior to the induction or immediately after intubation. A single dose of intravenous nicardipine or nimodipine could attenuate blood pressure elevations

without influencing the BIS during RSI [23]. There were no reports of unpleasant memories or recall stemming from RSI within 24 h following surgery. We did not measure the duration of the neuromuscular blockade in this study but no cases showed prolonged duration of neuromuscular blockade.

There are several limitations to this study. We could not obtain the measurement of CO or muscle blood flow during the induction of the anesthesia because of the cost to patients. Further studies with continuous measurement of CO and tissue perfusion may be necessary to determine the mechanism of action for pretreatment drugs on the onset time of rocuronium. Additionally, as we performed mask ventilation to preventing awakening and recall during RSI, there may be discrepancies between our study and the situation requiring RSI.

In conclusion, pretreatment or immediate intervention may be necessary to prevent cardiovascular instabilities after intubation for RSI. The onset time of rocuronium can be affected by prior administration of nicardipine and esmolol during RSI. Esmolol prolonged the onset time of rocuronium and disturbed the intubation conditions for RSI, despite preventing changes in HR. Nicardipine could be used to improve intubation conditions, accelerate the onset of rocuronium, and to prevent hypertension for RSI.

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