Excellent intubating conditions with remifentanyl–propofol and either low-dose rocuronium or succinylcholine

Excellentes conditions d'intubation avec le rémifentanyl-propofol et soit du rocuronium à faible dose ou de la succinylcholine

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Abstract

Purpose The shortest time to tracheal intubation, the best intubating conditions, and the shortest duration of muscle paralysis are achieved with succinylcholine. During a lidocaine–remifentanyl–propofol induction of anesthesia, we compared intubating conditions 90 s after administering low-dose rocuronium ($0.3 \text{ mg} \cdot \text{kg}^{-1}$) with intubating conditions 60 s after administering succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$.

Methods The randomized double-blind study included 184 healthy adult patients scheduled for elective surgery. Anesthesia was induced in all patients with lidocaine $1.5 \text{ mg} \cdot \text{kg}^{-1}$, remifentanyl $2 \mu\text{g} \cdot \text{kg}^{-1}$, and propofol $2 \text{ mg} \cdot \text{kg}^{-1}$ administered over 30 s. In one group, rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ was administered before the induction sequence, and in the other group, succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ was administered after the induction sequence. Laryngoscopy was attempted 90 s after rocuronium administration and 60 s after succinylcholine administration. Intubating conditions were assessed as excellent, good, or poor on the basis of ease of

laryngoscopy, position of the vocal cords, and reaction to insertion of the tracheal tube and cuff inflation.

Results There were 92 patients per group. In the rocuronium group, intubating conditions were excellent in 83 patients (90%), good in 8 (9%), and poor in 1 (1%), not significantly different from the intubating conditions in the succinylcholine group, which were excellent in 88 patients (96%), good in 3 (3%), and poor in 1 (1%) ($P = 0.3$).

Conclusion During a lidocaine–remifentanyl–propofol induction of anesthesia, rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ administered before the induction sequence provides intubating conditions comparable to those achieved with succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ administered after the induction sequence.

Résumé

Objectif La succinylcholine permet de réaliser l'intubation trachéale dans les plus courts délais, avec les meilleures conditions d'intubation et la durée la plus courte de paralysie musculaire. Au cours d'une induction de l'anesthésie avec lidocaïne-rémifentanyl-propofol, nous avons comparé les conditions d'intubation 90 sec après avoir administré du rocuronium à faible dose ($0,3 \text{ mg} \cdot \text{kg}^{-1}$) aux conditions d'intubation 60 sec après avoir administré de la succinylcholine à $1,5 \text{ mg} \cdot \text{kg}^{-1}$.

Méthode Au total, 184 patients adultes sains devant subir une chirurgie non urgente ont pris part à cette étude randomisée en double aveugle. L'anesthésie a été induite chez tous les patients avec de la lidocaïne ($1,5 \text{ mg} \cdot \text{kg}^{-1}$), du rémifentanyl ($2 \mu\text{g} \cdot \text{kg}^{-1}$) et du propofol ($2 \text{ mg} \cdot \text{kg}^{-1}$) administrés sur une période de 30 sec. Dans un groupe, du rocuronium ($0,3 \text{ mg} \cdot \text{kg}^{-1}$) a été administré avant la

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séquence d'induction, et dans l'autre groupe, de la succinylcholine ($1,5 \text{ mg} \cdot \text{kg}^{-1}$) a été administrée après la séquence d'induction. On a tenté une laryngoscopie 90 sec après l'administration de rocuronium et 60 sec après celle de succinylcholine. Les conditions d'intubation ont été évaluées comme étant excellentes, bonnes ou mauvaises selon la facilité de la laryngoscopie, la position des cordes vocales et la réaction à l'insertion de la sonde endotrachéale et au gonflement du ballonnet.

Résultats Chaque groupe comptait 92 patients. Dans le groupe rocuronium, les conditions d'intubation furent excellentes chez 83 patients (90 %), bonnes chez 8 (9 %), et mauvaises chez un patient (1 %), une différence non significative par rapport aux conditions d'intubation dans le groupe succinylcholine, lesquelles étaient excellentes chez 88 patients (96 %), bonnes chez 3 (3 %) et mauvaises chez un patient (1 %) ($P = 0,3$).

Conclusion Pendant l'induction de l'anesthésie avec lidocaïne-rémifentanyl-propofol, le rocuronium ($0,3 \text{ mg} \cdot \text{kg}^{-1}$) administré avant la séquence d'induction procure des conditions d'intubation comparables à celles obtenues avec de la succinylcholine ($1,5 \text{ mg} \cdot \text{kg}^{-1}$) administrée après la séquence d'induction.

The shortest time to tracheal intubation, the best intubating conditions, and the shortest duration of muscle paralysis are achieved with the depolarizing neuromuscular blocking agent, succinylcholine.¹ However, succinylcholine has serious side effects and is contraindicated in many clinical situations.² The low potency of the non-depolarizing agent, rocuronium, is associated with a rapid onset of action. For this reason, rocuronium has been recommended as a component of a rapid sequence induction of anesthesia at doses varying from 0.6 to $1.2 \text{ mg} \cdot \text{kg}^{-1}$ (2–4 times the effective dose for 95% twitch depression or 2 to $4 \times \text{ED}_{95}$) to obtain intubating conditions equivalent to those achieved with succinylcholine.^{3–7} However, such high doses of rocuronium have a prolonged duration of action,⁸ which may not be suitable for surgery of short duration. Kopman *et al.* demonstrated that lower doses of rocuronium ($1.5 \times \text{ED}_{95}$) provide clinically acceptable conditions for intubation 75 s after drug administration.⁹ The advantages of lower doses include a shorter clinical duration, the possibility to administer a reversal agent earlier or to avoid reversal altogether, and suitability for brief surgical procedures.¹⁰

In previous studies, a high percentage of acceptable intubating conditions have been obtained with a rocuronium dose as low as $0.3 \text{ mg} \cdot \text{kg}^{-1}$ or $1 \times \text{ED}_{95}$, in combination with alfentanil $10 \mu\text{g} \cdot \text{kg}^{-1}$ or remifentanyl infusion $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and propofol $2\text{--}2.5 \text{ mg} \cdot \text{kg}^{-1}$.^{10,11} However, these studies did not compare intubating

conditions with those obtained with the gold standard, succinylcholine. Therefore, we designed a prospective randomized double-blind study to evaluate intubating conditions following a low dose of rocuronium ($0.3 \text{ mg} \cdot \text{kg}^{-1}$) and to compare the results with intubating conditions following a dose of succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$.

Methods

After institutional review board approval and patients' written informed consent, we studied 189 male and female patients who were ASA physical status I to II, aged 18–60 years, and scheduled for elective orthopedic, gynecologic, and otorhinolaryngological ambulatory surgery. Exclusion criteria included a history of gastroesophageal reflux, hypertension, asthma, drug or alcohol abuse, cardiovascular disease, body mass index $>30 \text{ kg} \cdot \text{m}^{-2}$, neuromuscular disease or medication influencing neuromuscular transmission, and anticipated difficult intubation. Also excluded were patients with a contraindication to the use of succinylcholine, such as predisposition to malignant hyperthermia, decreased pseudocholinesterase activity or known genetic variation, and conditions causing susceptibility to succinylcholine-induced hyperkalemia (for example burn or denervation injury). Patients were recruited from October 2006 to December 2007.

No premedication was administered. A 20-G cannula was inserted into a vein in the dorsum of the hand. An intravenous infusion of lactated Ringer's solution was started before induction of anesthesia. Patients were randomly assigned to one of two groups by using a computer-generated table of random numbers. The rocuronium group ($n = 94$) received rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ before the induction sequence, and the succinylcholine group ($n = 95$) received succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ after the induction sequence. The first author (SMS) established the random allocation sequence. No method of restriction was implemented. The results of the randomization were concealed in opaque envelopes and were opened sequentially immediately before the start of preoxygenation.

All patients were monitored with a non-invasive blood pressure device, electrocardiogram, peripheral pulse oximetry, and capnography. Baseline heart rate (HR) and mean arterial pressure (MAP) were recorded. A Medfusion™ 3010 syringe pump (Medex Health Care Company, Duluth, GA, USA) containing remifentanyl $100 \mu\text{g} \cdot \text{mL}^{-1}$ was connected via a three-way stopcock located at the proximal end of the cannula. Another three-way stopcock was attached to the first one to allow for injection of propofol and other drugs used for induction of anesthesia. All patients were preoxygenated by tidal volume breathing using 100% oxygen at $8 \text{ L} \cdot \text{min}^{-1}$ for 3 min. Following

preoxygenation, patients in both groups received lidocaine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ over 5 s. Immediately afterward, patients in the rocuronium group received rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ over 5 s. Then a remifentanyl infusion was started to allow the administration of $2 \mu\text{g} \cdot \text{kg}^{-1}$ over 30 s. At the start of remifentanyl infusion, propofol $2 \text{ mg} \cdot \text{kg}^{-1}$ was injected via the second three-way stopcock over 15 s. In the succinylcholine group, after the injection of lidocaine, the remifentanyl–propofol combination was administered in the same manner as in the rocuronium group. Patients in the succinylcholine group received succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ over 5 s after the end of the remifentanyl infusion. All drugs were prepared and administered by an anesthesiologist not involved with intubation. Oxygen was delivered via a facemask until laryngoscopy was performed. Since fasciculations would identify succinylcholine as the drug being administered, the anesthesiologist performing and grading the intubating conditions was positioned with his back to the patient until just before the start of laryngoscopy.

Using a Macintosh 3 blade, direct laryngoscopy was started 60 s after the end of remifentanyl administration, which was 90 s after rocuronium administration in the rocuronium group and 60 s after succinylcholine administration in the succinylcholine group. Total induction time, defined as the interval from administering the first drug until the start of laryngoscopy, was the same in the two groups (100 s). A 7.0- or 8.0-mm tracheal tube was used for females and males, respectively. Intubating conditions, based on a scoring system proposed for good clinical research practice, were evaluated using the following variables¹²: ease of laryngoscopy, vocal cord position, and reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement-coughing). Each of these variables was rated as excellent, good, or poor. Intubating conditions were excellent if all variables were excellent; they were good if at least one variable was good and the rest were excellent, and they were poor if any variable was poor. The investigator performing the intubation and grading the intubating conditions was an experienced anesthesiologist who was blinded as to which group each patient had been assigned. Each laryngoscopy was graded using the standard Cormack and Lehane scoring system (1 = full view of the glottis; 2 = partial view of the glottis or arytenoids; 3 = only epiglottis visible; 4 = neither glottis nor epiglottis visible).¹³

Before induction of anesthesia, surface electrodes were placed over the ulnar nerve at the wrist. After loss of consciousness, the ulnar nerve was stimulated at the wrist with a square wave stimulus set at a current of 40 mA and duration of 0.2 ms. Each stimulus was delivered in a train-of-four (TOF) sequence and repeated every 12 s using a TOF-Guard peripheral nerve stimulator (Acceleromyograph, Biometer,

Organon Teknika NV, Belgium). At the time of intubation, an investigator recorded TOF ratio, which was displayed on the TOF monitor in the rocuronium group. To avoid vocal cord injury, tracheal intubation was not attempted if the vocal cords were fully closed. After intubation, anesthesia was maintained with 66% nitrous oxide in oxygen, isoflurane, and a remifentanyl infusion. If surgery required more muscle relaxation, additional boluses of rocuronium were given at the discretion of the anesthesiologist.

Measurements of HR and MAP were made immediately after induction, immediately after tracheal intubation, and 2 and 5 min after tracheal intubation. Ephedrine 6 mg *iv* was administered if MAP was decreased by more than 25% compared with baseline for 60 s, and atropine $10 \mu\text{g} \cdot \text{kg}^{-1}$ was given if HR was less than 50 beats min^{-1} . The patients were assessed the following day and checked specifically for awareness.

Our primary outcome measurement was the incidence of excellent intubating conditions. Secondary outcomes of interest were HR and MAP. It was assumed that excellent intubating conditions in the succinylcholine group would be almost 100%, and less than 10% difference (down to 90%) was of no clinical interest. With a 0.05 level of significance and 80% power, it was calculated that 92 patients were required in each group. Categorical data were expressed as numbers and percentages and analyzed using Chi-square or Fisher's exact test, as appropriate. Continuous data were expressed as mean (SD) and analyzed using Student's *t* test. A *P* value < 0.05 was considered to indicate a statistically significant difference.

Results

A total of 199 patients were screened for eligibility. Ten patients did not meet the inclusion criteria (three patients with gastroesophageal reflux, three patients with hypertension, and four patients with cardiovascular disease) and were excluded, leaving 189 patients to be randomized. Two patients in group rocuronium and three patients in group succinylcholine were excluded because of protocol violation (sequence of drug administration or dose not respected). Ninety-two patients in each group completed the trial.

The patients' characteristics were similar in both groups (Table 1). Tracheal intubation was successful on first attempt in all patients. The overall intubating conditions did not differ between the two groups (*P* = 0.3). Intubating conditions were excellent in 83 (90%; 95% confidence interval (CI): 84–96) patients in the rocuronium group and 88 (96%; 95% CI: 91–100) patients in the succinylcholine group (*P* = 0.15) (Table 2). Only one patient in each group had poor intubating conditions. The remainder was rated as good. The various intubating scores are shown in Table 2,

Table 1 Patients' characteristics

	Rocuronium group (<i>n</i> = 92)	Succinylcholine group (<i>n</i> = 92)
Age (year)	36 (10)	38 (12)
Weight (kg)	71 (16)	72 (17)
Height (cm)	166 (11)	164 (8)
Gender (M/F)	27/65	33/59
Smoking (<i>n</i>)	21	30

Data are means (SD) or numbers

with no statistical significance between the two groups except for cough that occurred more frequently in the rocuronium group ($P = 0.034$).

Seven patients in the rocuronium group and eight patients in the succinylcholine group had a Cormack-Lehane grade of 2, while two patients in the rocuronium group and two patients in the succinylcholine group had a Cormack-Lehane grade of 3. In the rocuronium group, mean TOF ratio was 65 (16%) at the time of intubation.

Baseline values for MAP were similar in both groups (90 [13] and 92 [13] mmHg in the rocuronium and the succinylcholine groups, respectively). The lowest MAP values recorded were 64 (11) and 62 (12) mmHg, respectively, with no statistically significant difference between groups. Heart rate was also similar at baseline (85 [18] and 80 [15] beats $\cdot$ min⁻¹, respectively). However, the lowest HR value recorded was less in the succinylcholine group compared with the rocuronium group (67 [12] vs. 74 [13] beats min⁻¹, respectively; $P < 0.001$). In the succinylcholine group, 12 patients developed a decrease of MAP by more than 25% from baseline value for 60 s, necessitating

the use of ephedrine, whereas in the rocuronium group, four patients required ephedrine ($P = 0.067$). Atropine was used in four patients in the succinylcholine group and in none of the patients in the rocuronium group ($P = 0.129$).

No patient in either group experienced laryngospasm, bronchospasm, hypoxemia, or any other significant complication. At the 24-h postoperative visit, awareness was not reported by any of the patients.

Discussion

Non-depolarizing muscle relaxants have been commonly used at doses equal to or greater than twice the ED₉₅ to achieve adequate intubating conditions. However, low potency drugs with rapid onset profiles might provide clinically acceptable conditions at lower multiples of ED₉₅.^{9–11} In patients undergoing elective surgery, our report shows that a low dose of rocuronium 0.3 mg $\cdot$ kg⁻¹ supplementing a lidocaine–remifentanyl–propofol combination provides excellent tracheal intubating conditions in 90% of patients, a rate similar to that achieved by succinylcholine 1.5 mg $\cdot$ kg⁻¹ (96%) while using the same anesthetic technique and a similar total induction time of 100 s.

Many studies have previously shown that tracheal intubation may be accomplished without a neuromuscular blocking agent when anesthesia is induced with propofol and a short-acting opioid such as remifentanyl.^{14–16} However, there are still patients with unacceptable responses to intubation even after high doses of remifentanyl without a neuromuscular blocking agent. When Stevens and

Table 2 Scoring criteria at tracheal intubation (number of patients, %)

Variables	Excellent	Good	Poor	<i>P</i>
<i>Laryngoscopy</i> ^a	Easy	Fair	Difficult	0.25
Rocuronium group	92 (100%)	0	0	
Succinylcholine group	89 (97%)	3 (3%)	0	
<i>Vocal cords position</i>	Abducted	Intermediate/moving	Closed	0.49
Rocuronium group	92 (100%)	0	0	
Succinylcholine group	90 (98%)	2 (2%)	0	
<i>Coughing at tracheal intubation</i>	None	Slight ^b	Vigorous/sustained ^c	0.034
Rocuronium group	83 (90%)	8 (9%)	1 (1%)	
Succinylcholine group	90 (98%)	1 (1%)	1 (1%)	
<i>Overall assessment</i>				0.30
Rocuronium group	83 (90%)	8 (9%)	1 (1%)	
Succinylcholine group	88 (96%)	3 (3%)	1 (1%)	

^a Laryngoscopy: Easy: jaw relaxed, no resistance to blade insertion; Fair: jaw not fully relaxed, slight resistance to blade insertion; Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy

^b One to two weak contractions or movement for less than 5 s

^c More than two contractions and/or movement for longer than 5 s. Statistical significance was noted at coughing between the two groups

Wheatley used remifentanyl $2 \mu\text{g} \cdot \text{kg}^{-1}$ in combination with propofol $2 \text{ mg} \cdot \text{kg}^{-1}$, excellent intubating conditions did not exceed 50%.¹⁵ In another study, Klemola *et al.* reported that the administration of remifentanyl $4 \mu\text{g} \cdot \text{kg}^{-1}$ with propofol $2.5 \text{ mg} \cdot \text{kg}^{-1}$ provided excellent intubating conditions in only 60% of patients.¹⁶ Also, vocal cord sequelae occur more frequently in patients for whom tracheal intubation is attempted without neuromuscular blocking agents. Supplementing a propofol-opioid induction regimen with a non-depolarizing agent improves the quality of tracheal intubation and decreases postoperative hoarseness.¹⁷

It has been previously demonstrated that rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ with propofol and an opioid allows adequate intubating conditions. During induction of anesthesia with propofol $2.5 \text{ mg} \cdot \text{kg}^{-1}$ and alfentanil $10 \mu\text{g} \cdot \text{kg}^{-1}$, Barclay *et al.* evaluated intubating conditions at 120 s after rocuronium 0.1 and $0.3 \text{ mg} \cdot \text{kg}^{-1}$ and after saline. Acceptable intubating conditions, defined as excellent or good conditions, could be achieved in a large proportion (18 out of 20 patients) only after a $0.3 \text{ mg} \cdot \text{kg}^{-1}$ dose of rocuronium.¹¹ Also, Schlaich *et al.* examined intubating conditions at 180 s with different doses of rocuronium (0.3, 0.45, or $0.6 \text{ mg} \cdot \text{kg}^{-1}$) or saline after induction of anesthesia with a remifentanyl infusion at a rate of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and propofol $2 \text{ mg} \cdot \text{kg}^{-1}$. They rated conditions as excellent in 13 of the 30 patients (43%) after rocuronium $0.3 \text{ mg} \cdot \text{kg}^{-1}$ and in only two of 30 patients (6%) when rocuronium was omitted.¹⁰ Unlike these studies, our aim was to reproduce, as closely as possible, the characteristics of succinylcholine paralysis, i.e., excellent intubating conditions with short onset and duration of block. For this reason, we elected to attempt intubation only 90 s after administering rocuronium and 60 s after administering propofol-remifentanyl.

Kopman *et al.* obtained clinically acceptable intubating conditions in all patients with laryngoscopy being attempted 75 s after rocuronium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ was administered with an induction regimen including alfentanil $12.5 \mu\text{g} \cdot \text{kg}^{-1}$ and propofol $2 \text{ mg} \cdot \text{kg}^{-1}$.⁹ We used a smaller dose ($0.3 \text{ mg} \cdot \text{kg}^{-1}$) of rocuronium with a longer interval to laryngoscopy (90 s), allowing more time to achieve peak neuromuscular effects. Although the total induction time was similar between the two groups (100 s), intubation in the rocuronium group was attempted at a different time than in the succinylcholine group (90 s vs. 60 s after drug administration). Also, rocuronium, not succinylcholine, was given before the induction sequence. In fact, the delayed onset of such a small dose was circumvented by its administration before the remifentanyl-propofol combination in order to achieve the best endotracheal intubating conditions in the rocuronium group. A possible problem with such a technique is that patients

might become paralyzed before they are anesthetized. However, none of the patients had an unpleasant experience caused by this dose. The onset time of neuromuscular block after a small dose of rocuronium is longer than after a larger dose. Also, propofol was given immediately after injection of rocuronium. The 95% CI of the risk of developing awareness in patients who received low dose rocuronium before the hypnotic, based on zero episodes in ~100 patients, is 0–3%.¹⁸

The TOF ratio at the adductor pollicis was 65 (16%) at the time of intubation in the rocuronium group. However, the intubating conditions are related more closely to the degree of neuromuscular block of the laryngeal adductor muscles than the degree of blockade usually monitored at the adductor pollicis.⁸ The onset of neuromuscular block (interval from injection to maximal T_1 blockade) is more rapid in the muscles that are relevant to obtaining optimal intubating conditions, i.e., laryngeal adductors, diaphragm, and masseter than in the adductor pollicis muscles.¹⁹ Thus, the onset time of neuromuscular block at the adductor pollicis should not be considered as a meaningful quantifiable endpoint defining optimal intubating conditions.²⁰

The usual increase in blood pressure and HR following laryngoscopy and tracheal intubation was not observed in the two groups. More bradycardia followed induction of anesthesia and tracheal intubation in the succinylcholine group compared to the rocuronium group. However, the difference between the two groups was small and not clinically significant.

In conclusion, during a lidocaine-remifentanyl-propofol sequence for induction of anesthesia, a low dose of rocuronium ($0.3 \text{ mg} \cdot \text{kg}^{-1}$) provides excellent intubating conditions (90%) similar to those achieved with succinylcholine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ (96%) with a similar total induction time of 100 s. With such a technique, we were able to reproduce the advantages of succinylcholine, such as a short time to intubation and excellent intubating conditions. This technique could be applied for brief surgical procedures or whenever the anticipated duration of surgery is uncertain.

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Conflicts of interest None declared.

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