

Anesthesiology
1999; 91:1311-7
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Comparison of the Intubation Conditions Provided by Rapacuronium (ORG 9487) or Succinylcholine in Humans during Anesthesia with Fentanyl and Propofol

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Background: Currently, the only approved muscle relaxant with a rapid onset and short duration of action is succinylcholine, a drug with some undesirable effects. Rapacuronium is an investigational nondepolarizing relaxant that also has a rapid onset and short duration and consequently should be compared with succinylcholine in its ability to facilitate rapid tracheal intubation.

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Methods: This prospective, randomized clinical trial involved 336 patients. Anesthesia was induced with fentanyl and propofol and either 1.5 mg/kg rapacuronium or 1.0 mg/kg succinylcholine. The goal was to accomplish tracheal intubation by 60 s after administration of the neuromuscular blocking drug. Endotracheal intubation was performed, and conditions were graded by a blinded investigator. Recovery of neuromuscular function was assessed by electromyography.

Results: Intubation conditions were evaluated in 236 patients. Intubation by 60 s after drug administration occurred in 100% of patients with rapacuronium and in 98% with succinylcholine. Intubation conditions were excellent or good in 87% of patients with rapacuronium and in 95% with succinylcholine ($P < 0.05$). The time (median and range) to the first recovery of the train-of-four response was 8.0 (2.8–20.0) min with rapacuronium and 5.7 (1.8–17.7) min with succinylcholine ($P < 0.05$). The overall incidence of adverse effects was similar with both drugs.

Conclusions: A 1.5-mg/kg dose of rapacuronium effectively facilitates rapid tracheal intubation. It can be considered a valid alternative to 1.0 mg/kg succinylcholine for this purpose. (Key words: Adverse events; cardiovascular; neuromuscular block.)

IN 1975, the need for a nondepolarizing relaxant with a fast onset and short duration of action was described.¹ Currently, there are no fast-onset, short-duration nondepolarizing muscle relaxants available in clinical practice. Rapacuronium is an investigational, aminosteroid neuromuscular blocking drug (muscle relaxant), the 16-N-allyl, 17- β -propionate analog of vecuronium.² It has low potency (estimated ED₉₀, 1.15 mg/kg) and a rapid onset and short duration of action.²⁻⁴ Rapacuronium is the first type A relaxant to reach an advanced stage of clinical development.

In a dose of 1.5 mg/kg, rapacuronium has an onset of action ranging from 83 to 114 s³⁻⁵ and a duration until 25% recovery of control twitch tension ranging from 8 to 14 min.^{3,4,6} In current practice, the only approved muscle relaxant with a similar rapid onset and short duration

of action is succinylcholine. However, succinylcholine has several adverse effects that range from mild (*e.g.*, myalgia) to life-threatening (*e.g.*, hyperkalemia and malignant hyperthermia).⁷ These adverse effects are related to the depolarizing mechanism of action of succinylcholine and have fueled the efforts to develop a nondepolarizing alternative. A previous, abbreviated study suggested that 1.5 mg/kg rapacuronium has an onset similar to that of 1.0 mg/kg succinylcholine and provides comparable conditions for tracheal intubation.³ This multicenter study expands on that earlier work by comparing, in a large number of patients, the ability of rapacuronium and succinylcholine to facilitate rapid tracheal intubation.

Methods

This phase III, prospective, randomized, patient- and assessor-blinded, multicenter study was approved by the investigational review boards at each of the five institutions involved. All patients gave written informed consent to participate. Patients were aged ≥ 18 yr and were American Society of Anesthesiologists physical class 1 to 4. Approximately 20% of subjects recruited were to be older than 65 yr (geriatric group). Potential participants in the study were excluded if they took medications or had a disease process that might affect neuromuscular function, or if their medical history or physical examination suggested possible difficulty with airway management.

Patients were premedicated with lorazepam 1-2 mg orally or midazolam 1-5 mg intravenously. In the operating room, routine vital function monitoring, including electrocardiography and noninvasive blood pressure measurement, was commenced. Each patient then breathed 100% oxygen from the anesthesia circuit *via* a face mask (preoxygenation), and 2-5 $\mu\text{g}/\text{kg}$ fentanyl was administered intravenously. Preoxygenation was continued for 3 min, then 1-3 mg/kg propofol was administered intravenously. When the patient lost consciousness, neuromuscular function monitoring by electromyography of the adductor pollicis muscle (Relaxograph; Datex Instrumentarium Inc., Helsinki, Finland) was begun. When a stimulation sequence was delivered and an appropriate neuromuscular response was observed, the muscle relaxant was administered. Each patient was assigned to receive either 1.5 mg/kg rapacuronium ($1.3 \cdot \text{ED}_{90}$)² or 1.0 mg/kg succinylcholine according to a predetermined randomization sequence.

Table 1. Criteria for Grading Intubation Conditions

	Excellent	Good	Poor
Vocal cord position	Abducted	Intermediate	Adducted
Vocal cord movements	None	Moving	Closing
Ease of laryngoscopy	Easy	Fair	Resistant
Airway reaction	None	Diaphragm	Sustained > 10 s
Movement of limbs	None	Slight	Vigorous

Because the observation of fasciculations would identify the drug administered as succinylcholine, the anesthesiologist performing and grading intubation turned to face the patient just before beginning the intubation sequence in an attempt to minimize the chance of observing fasciculations. The tracheal intubation sequence was begun between 40 and 45 s after administration of the muscle relaxant. The patient's head was positioned, laryngoscopy was commenced at 50 s, and tracheal intubation was accomplished 60 s after relaxant administration. The scheme for grading conditions for tracheal intubation was based on the criteria of good clinical research practice (table 1).⁸ If tracheal intubation could not be performed within 60 s because of anatomic problems that were independent of the degree of muscle relaxation, this was recorded. To limit variability, tracheal intubation was performed by experienced anesthesiologists at each study site. The investigator performing the intubation and grading intubation conditions was blinded as to which neuromuscular blocking drug had been administered. Intubation conditions were classified as acceptable if they were graded excellent or good and as unacceptable if they were graded poor or if intubation was not possible.

After tracheal intubation, anesthesia was maintained with nitrous oxide 60-70% and an infusion of propofol plus supplemental boluses of fentanyl, with the dosing adjusted according to the patient's clinical need. If neuromuscular block was required for the remainder of the surgical procedure, rocuronium or another approved muscle relaxant was administered regardless of the level of recovery from the study drug.

Recovery from neuromuscular block was monitored with the Relaxograph. Supramaximal stimuli (0.2 ms duration) were applied to the ulnar nerve at the wrist in a train-of-four sequence at 2 Hz; trains of stimuli were repeated at 10-s intervals. Stimulation was begun immediately after induction of anesthesia. The resulting compound action potential from the adductor pollicis was recorded. Because of the need to proceed to rapid tracheal intubation, there was insufficient time to allow

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Table 2. Demographic Characteristics of Patients

Variable	Treatment Group			
	Rapacuronium		Succinylcholine	
	Adult (n = 133)	Geriatric (n = 36)	Adult (n = 131)	Geriatric (n = 36)
Age (yr) [median (range)]	41 (18-64)	72 (65-92)	40 (18-64)	72 (65-86)
Weight (kg) [median (range)]	71 (46-143)	76 (34-109)	72 (47-125)	76 (49-95)
Gender [N (%)]				
Male	41 (31)	22 (61)	48 (37)	17 (47)
Female	92 (69)	14 (39)	83 (63)	19 (53)
ASA class [N (%)]				
1	72 (54)	4 (11)	64 (49)	1 (3)
2	51 (38)	21 (58)	59 (45)	27 (75)
3	9 (7)	11 (33)	8 (6)	8 (22)
4	1 (1)	0	0	0
Fentanyl dose ($\mu\text{g}/\text{kg}$)		2.6 (0.6-7.9)		2.5 (0.1-6.1)
Propofol dose (mg/kg)		2.1 (0.5-4.0)		2.0 (0.2-4.1)

stabilization of the electromyography response before administration of the neuromuscular blocking drug; therefore, a control value for the first train-of-four response (T1) was not obtained (uncalibrated mode). The time of initial neuromuscular recovery was defined as the point after complete block when the first T1 response returned. If complete block did not occur, recovery was not measured.

Each patient was observed for the adverse affects of flushing, wheezing, and blood pressure and heart rate changes at 1-min intervals for 10 min after administration of the neuromuscular-blocking drug. Significant adverse events in the perioperative and postoperative periods were recorded.

The demographic characteristics of the rapacuronium and succinylcholine groups were compared by two-way analysis of variance or chi-square test as appropriate. Comparison of patients with respect to the grade of intubation conditions was conducted using the Cochran-Mantel-Hanszel test. For cardiovascular variables, rank transformation was applied to the percent changes from baseline (prerelaxant) at 1, 2, 3, 4, 5, and 10 min. Repeated-measures analysis of variance was applied to the rank transformed data.

The sample size of each group required to detect a 10% difference in the incidence of the different grades of intubation conditions between rapacuronium and succinylcholine was estimated to be 140. This estimate was based on the ability to detect an absolute difference of 10% between the two groups with a power of 80%, assuming that the percentage of subjects with accept-

able intubation conditions in the succinylcholine group would be 96%, and an α value of 0.05.

Results

A total of 336 patients (56 at one site and 70 at each of the other four) aged 18-92 yr were enrolled in the study. Patient demographic variables, age, weight, gender, and

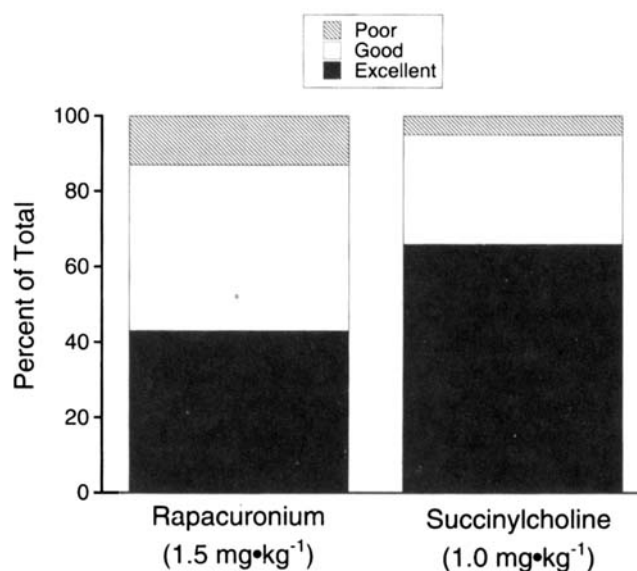


Fig. 1. Intubating conditions with rapacuronium or succinylcholine: black column = excellent; white column = good; hatched column = poor. Two patients in the succinylcholine group who experienced intubation failure at 60 s are represented as poor conditions.

Table 3. Intubation Conditions at 60 s: Distribution by Age Group

Intubation Grade	Adult*		Geriatric	
	Rapacuronium (n = 98) [n (%)]	Succinylcholine (n = 84) [n (%)]	Rapacuronium (n = 26) [n (%)]	Succinylcholine (n = 28) [n (%)]
Excellent	40 (41)	52 (62)	13 (50)	22 (79)
Good	43 (44)	26 (31)	12 (46)	6 (21)
Poor	15 (15)	4 (5)	1 (4)	0
Impossible	0	2 (2)	0	0
Acceptable	83 (85)	78 (93)	25 (96)	28 (100)
Unacceptable	15 (15)	6 (7)	1 (4)	0

* $P < 0.05$, rapacuronium versus succinylcholine for acceptable (excellent or good) intubation conditions.

American Society of Anesthesiologists physical class are summarized by drug treatment group (table 2). There were no demographic differences between the two groups. The primary outcome variable, intubation conditions, was analyzed formally in a total of 236 patients (fig. 1). Intubation conditions were not analyzed for 100 patients because of protocol violations such as administration of anesthesia induction drugs outside of the designated time or dose ranges, incorrect timing of the sequence of intubation, or administration of relaxant in violation of the randomization schedule. The number of excluded subjects was in large part because of a systematic documentation error at one of the study sites, which precluded use of that data even though the protocol was followed correctly. These excluded subjects were replaced by additional enrollment at the other sites.

Intubation was accomplished by 60 s in 100% of patients with rapacuronium and 98% of patients with succinylcholine. Tracheal intubation could not be accomplished by 60 s in two patients in the succinylcholine group because of unanticipated difficulty in viewing the larynx, and both were graded as impossible. For both patients, intubation was accomplished at the second attempt, one with and one without administration of supplemental muscle relaxant. The proportion of assessable patients (adult and elderly combined) with intubation conditions graded excellent or good was 87% with rapacuronium and 95% with succinylcholine ($P < 0.05$). Fewer patients had excellent intubation conditions with rapacuronium (43%) than with succinylcholine (67%; $P < 0.05$). The incidence of poor (poor plus impossible grade combined) conditions was not different between the drugs. Intubation conditions broken down by drug treatment group and age are listed in table 3.

Initial recovery of T1 (median and range) occurred in 8.0 (2.8–20.0) min for rapacuronium ($n = 75$) and 5.7 (1.8–17.7) min for succinylcholine ($n = 89$; $P < 0.05$).

The median time until the train-of-four ratio recovered to 0.7 after administration of rapacuronium ($n = 77$) was 34.2 (13.8–97.3) min. The median time until recovery of T1 twitch tension reached a maximum after succinylcholine ($n = 39$) occurred at 13.8 (4.0–31.7) min.

Changes in heart rate and mean arterial pressure after initial administration of muscle relaxant are illustrated in figures 2 and 3. The mean percentage increase in heart rate in the 10 min after drug administration was approximately 10% greater for rapacuronium than succinylcholine ($P < 0.01$). The incidence of a heart rate change $> 30\%$ was higher with rapacuronium than succinylcholine: 41% and 20%, respectively ($P < 0.05$).

The greatest change in mean arterial pressure was observed at 1 and 10 min after administration for both drugs. More patients had a $> 30\%$ increase in mean

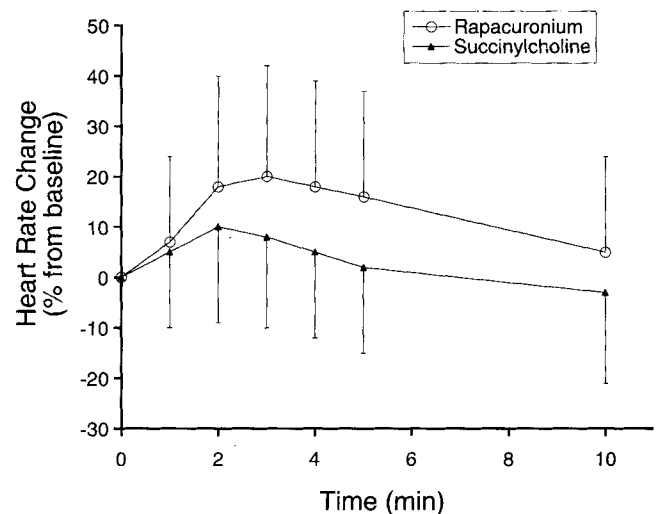


Fig. 2. Percentage change from baseline of heart rate in the 10 min after administration of 1.5 mg/kg rapacuronium or 1.0 mg/kg succinylcholine. Data points are means, and error bars (one direction only for clarity) are 1 SD. Tracheal intubation occurred approximately at the 1-min time point.

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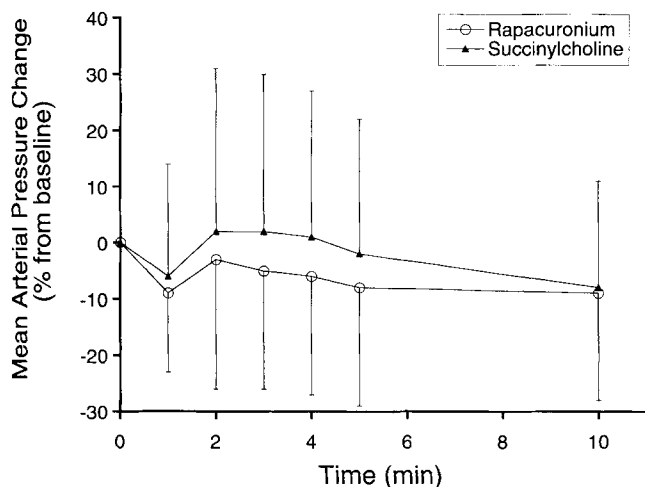


Fig. 3. Percentage change from baseline of mean arterial pressure in the 10 min after administration of 1.5 mg/kg rapacuronium or 1.0 mg/kg succinylcholine. Data points are means, and error bars (one direction only for clarity) are 1 SD. Tracheal intubation occurred approximately at the 1-min time point.

arterial pressure after succinylcholine administration than after rapacuronium administration: 26% and 14%, respectively ($P < 0.05$). Mean arterial pressure in the 10 min after drug administration decreased approximately 6% more after rapacuronium administration than after succinylcholine administration ($P < 0.05$). The number of patients with a $> 30\%$ increase in heart rate and $> 30\%$ decrease in mean arterial pressure was seven for rocuronium and zero for succinylcholine ($P < 0.05$).

Adverse events were evaluated for all 336 patients. The incidence of adverse events was comparable between the two drug treatment groups. A total of 158 events was reported in 99 patients. These adverse events were considered drug related in 21 cases for rapacuronium and 9 cases for succinylcholine. The most common adverse event was hypotension: 12% and 11% incidence for rapacuronium and succinylcholine, respectively. Bronchospasm (defined as wheezing on chest auscultation) occurred in five patients in the rapacuronium group and two in the succinylcholine group. Only one patient had no factor (e.g., smoking) predisposing to bronchospasm. For six patients, the bronchospasm was mild and resolved either spontaneously ($n = 2$) or after a single administration of inhaled β -agonist bronchodilator ($n = 4$). In the remaining patient (rapacuronium group), bronchospasm was of moderate severity and required administration of several doses of inhaled β -agonist bronchodilator and 100 mg hydrocortisone intravenously.

There was a total of 14 serious adverse events (7 in each drug treatment group; defined as any experience

that was either fatal, life-threatening, or permanently disabling, or that involved prolonged hospitalization or drug overdose) reported in 10 patients. Only one of these events, severe hypotension after rapacuronium administration, was considered drug-related.

Discussion

Rapacuronium 1.5 mg/kg and succinylcholine 1.0 mg/kg facilitated rapid tracheal intubation in 100% and 98% of patients, respectively. Thus, rapacuronium can be regarded as comparable to succinylcholine in overall success rate of intubation within 60 s. The principal difference between rapacuronium and succinylcholine was in the quality of intubation conditions, which were slightly, but significantly, superior after succinylcholine administration.

These comparisons are similar to those reported by Sparr *et al.*,⁹ who found that the incidence of acceptable intubation conditions was 8.1% greater with succinylcholine 1.0 mg/kg than with rapacuronium 1.5 mg/kg (97.4% vs. 89.4%, respectively).⁹ In that study, two anesthetic induction techniques (fentanyl/thiopental sodium or alfentanil/propofol) were used but were associated with similar intubation conditions. Because our results with a third anesthetic induction technique (fentanyl/propofol) are similar to those of that earlier study, it is likely that the difference between intubation conditions with succinylcholine and rapacuronium is independent of anesthetic drugs used for induction.

A partial explanation for different intubation conditions between the drugs is the difference in the levels of neuromuscular block each produces at the laryngeal muscles. A 1.0-mg/kg dose of succinylcholine will produce $> 99\%$ block of the laryngeal muscles,¹⁰ but 1.5 mg/kg rapacuronium will produce only 86% block.¹¹ There are several possible strategies by which the incidence of acceptable intubation conditions with rapacuronium may be increased.

First, a larger dose of rapacuronium could be administered. Doses of 2.0 and 2.5 mg/kg have been studied, and improved intubation conditions may be possible with these doses.⁶ However, the use of larger doses results in a longer duration of action, particularly in the elderly.⁶ A second strategy might be to use the technique of priming, but this is associated with a risk of premature weakness, diminished pulmonary function, and patient distress.¹²

Third, intubation conditions may be improved by ma-

nipulation of the drugs used for induction of anesthesia. The quality of intubation is enhanced by increasing doses of opioid^{13,14}; however, the utility of this approach may be limited by prolonged respiratory depression if large doses of fentanyl are administered. The use of alfentanil or remifentanil may enhance conditions for intubation without prolonged respiratory depression.^{15,16} Use of a different induction drug is unlikely to enhance intubation because propofol, in the doses used, seems optimal in this respect.¹⁶

Rapid onset is only one facet of the time course of action of rapacuronium; it also has a short duration, with an initial recovery close to that observed with succinylcholine. The significance of the difference between initial recovery time of 8.0 min for rapacuronium compared with 5.7 min for succinylcholine depends on the clinical situation. If the primary clinical consideration is for rapid recovery to allow flexibility in deciding whether to continue the neuromuscular block, then the difference between these two drugs is of little consequence. Alternatively, if the clinical situation is one in which recovery of neuromuscular function is essential for patient safety, for example, when the patient's trachea cannot be intubated,¹⁷ then the differences between the drugs may be important. There are some data suggesting that rapacuronium can be rapidly and effectively reversed by administration of neostigmine shortly after onset of block.^{3,18} This possibility requires further study before its clinical utility can be judged.

In general, the adverse effects evaluated in this study were comparable for rapacuronium and succinylcholine. The main difference between the drugs was the greater incidence of tachycardia with rapacuronium. This tachycardia may be related to the low potency of rapacuronium and the need to administer large doses. Rapacuronium does not inhibit noradrenaline reuptake, and its vagal-to-neuromuscular blocking ratio is 3.0,¹⁹ which is the same ratio as that for pancuronium but significantly less than that for vecuronium.²⁰ Consequently, some mild vagolytic effect might occur with rapacuronium 1.5 mg/kg.

The incidence of bronchospasm was not different between rapacuronium ($n = 5$) and succinylcholine ($n = 2$). Our study design did not allow us to determine if the bronchospasm was truly caused by the drugs themselves or by the performance of tracheal intubation with a light level of anesthesia.

We did not record other adverse events such as post-operative myalgia or evidence of muscle injury. Patients randomized to receive succinylcholine were not pretreated with a small dose of nondepolarizing relaxant;

therefore, it is likely that a significant proportion of these patients would have had succinylcholine-induced myalgia.²¹ Such myalgia does not occur after administration of nondepolarizing relaxants.^{22,23} Succinylcholine can also produce muscle damage, as indicated by increases in serum creatine kinase and myoglobinemia.^{21,24,25} The muscle damage may occasionally be sufficient to produce rhabdomyolysis and acute renal failure.^{26,27}

In a study of this size, we would not expect to observe the more serious but rare side effects of succinylcholine, namely, hyperkalemia with cardiac arrest,²⁸ triggering of malignant hyperthermia,²⁹ muscle contracture in patients with myotonia,³⁰ and masseter spasm in children.³¹ These adverse effects are caused by the depolarizing action of succinylcholine and should not occur with rapacuronium.

Our results are relevant to the use of rapacuronium for "rapid-sequence" tracheal intubation. The principal difference between the design of this study and the technique of rapid-sequence tracheal intubation is that cricoid pressure was not used.²⁰ Cricoid pressure enhances the view at laryngoscopy, and its use might have improved our intubation conditions.^{32,33} Even without the use of cricoid pressure, rapid tracheal intubation was achieved in all patients who received rapacuronium. This observation suggests that rapacuronium would be an effective alternative to succinylcholine for rapid-sequence tracheal intubation.

We chose the 1.0-mg/kg dose of succinylcholine because it is the recommended standard for facilitation of rapid tracheal intubation. The 1.5-mg/kg dose of rapacuronium was chosen because it has been shown to be adequate to facilitate rapid tracheal intubation^{3,6} and to have a duration of action < 20 min in both the young and the elderly.⁶ Smaller doses will not provide as good intubation conditions, and larger doses have a longer duration.⁶

Because the assessment of intubation conditions is subject to bias, the anesthesiologist performing the intubation was blinded as to which drug was administered. Of particular concern was the possibility that the observation of fasciculations would identify the drug administered as succinylcholine. It would have been possible to abolish the fasciculations by administering a defasciculating dose of nondepolarizing relaxant before succinylcholine administration and saline before rapacuronium administration. However, this technique is not foolproof because fasciculations are not always abolished, and patient complaints of diplopia or muscle weakness produced by the defasciculating drug would also have rendered the study unblinded. We cannot rule

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out some observer bias, but we believe that it was minimal and had no significant effect on the results.

In conclusion, we have demonstrated that 1.5 mg/kg rapacuronium effectively facilitates rapid tracheal intubation. Although it provides slightly inferior intubation conditions to 1.0 mg/kg succinylcholine, in many clinical conditions rapacuronium can be an effective alternative to succinylcholine and will not subject patients to the risk of adverse events associated with succinylcholine's depolarizing mechanism of action.

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