A comparison of tubocurarine, rocuronium, and cisatracurium in the prevention and reduction of succinylcholine-induced muscle fasciculations

CPT Cybil A. True, CRNA, MSN, USA, AN
Fort Sam Houston, Texas

CPT Pamela J. Carter, CRNA, MSN, USA, AN
Yongsan Army Garrison, South Korea

Fasciculations are a common side effect of the use of succinylcholine for tracheal intubation. Many anesthesia care providers prefer to prevent them due to a possible association between fasciculations and increased intracranial and intraocular pressures. The purpose of this study was to compare the effectiveness of tubocurarine, rocuronium, and cisatracurium in the prevention and reduction of succinylcholine-induced muscle fasciculations. The study was a prospective, randomized, double-blind, clinical drug comparison.

We randomly assigned 40 subjects to 1 of 4 pretreatment groups. Fasciculations were graded on a 4-point scale. A Kruskal-Wallis analysis of variance, used to analyze data collected from the fasciculation scale, demonstrated there was no statistically significant difference in efficacy between tubocurarine and rocuronium for defasciculation or between cisatracurium and saline for defasciculation. Significant differences were shown between the tubocurarine and cisatracurium groups and between the rocuronium and cisatracurium groups. Rocuronium is equally as efficacious as tubocurarine for defasciculation. Therefore, rocuronium is a valid alternative to tubocurarine for defasciculation. Cisatracurium is inferior to rocuronium and tubocurarine for defasciculation. Therefore, the use of cisatracurium is not recommended for defasciculation.

Key words: Cisatracurium, defasciculation, fasciculations, rocuronium, tubocurarine.

Fasciculations are visible muscular contractions resulting from asynchronous firing of muscle fibers in millions of motor units.[1,2] During anesthesia use, fasciculations arise from the prejunctional action of depolarizing muscle relaxants, specifically succinylcholine. Succinylcholine (SCh) is the only depolarizing muscle relaxant used to facilitate tracheal intubation.

Although fasciculations are a relatively benign side effect of succinylcholine, most anesthesia care providers prefer to prevent them due to a possible association between fasciculations and postoperative myalgia;[1] but a firm relationship has not been supported consistently.[3] The use of succinylcholine also produces other undesirable effects in addition to fasciculations, such as increased intracranial and intraocular pressure, hyperkalemia, myoglobinuria, and increased creatinine kinase levels.[4] Because of the risk of rhabdomyolysis, hyperkalemia, and cardiac arrest in children with undiagnosed myopathies, succinylcholine is contraindicated in the routine anesthetic care for children and adolescents.[2]

Preliminary evidence shows that side effects such as fasciculations are minimized by precurarization with a small dose of a nondepolarizing muscle relaxant (NDMR) to suppress fasciculations;[5] therefore, we compared the efficacy of 3 NDMRs for reducing succinylcholine-induced muscle fasciculations: tubocurarine, rocuronium, and cisatracurium.

Tubocurarine is considered the "gold standard" NDMR used for defasciculation, and it is the NDMR of choice with many anesthesia care providers.[1] The side effects of tubocurarine include histamine release, possible hypotension, and possible bronchospasm and have prompted research regarding the efficacy of other NDMRs that have fewer serious side effects and are more effective for defasciculation.

Rocuronium and cisatracurium are newer NDMRs. Many studies have compared rocuronium with tubocurarine.[3,6] Rocuronium is the least potent NDMR in use, but it has a rapid onset of action, which is desirable for defasciculation. There is less literature regarding the use of cisatracurium for defasciculation. Cisatracurium has the advantage of not causing histamine release; however, it has a slower onset of action than tubocurarine.[7]

A physiological model focusing on the neurons and neurotransmitters of the neuromuscular junction pro-

vides a useful framework to examine the cause and prevention of succinylcholine-induced muscle fasciculations. The model centers on the impact of depolarizing muscle relaxants and NDMRs in changing the actions of the neurons at the neuromuscular junction.

The normal action at the neuromuscular junction is represented in Figure 1. Acetylcholine binds at postsynaptic nicotinic muscle acetylcholine receptors on skeletal muscle, which causes contraction. If an NDMR is introduced, it will compete with acetylcholine for binding sites at the postsynaptic nicotinic muscle acetylcholine receptors. The binding of the NDMR causes skeletal muscle relaxation. Nondepolarizing muscle relaxants also have some degree of presynaptic activity, which is important for preventing fasciculations.

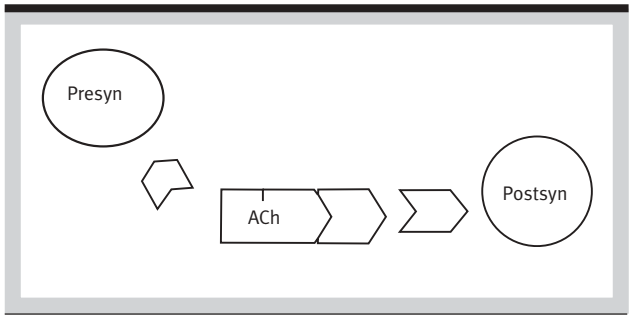
Depolarizing muscle relaxants such as succinylcholine bind presynaptically and postsynaptically to nicotinic acetylcholine receptors, but the presynaptic binding is thought to be associated with fasciculations.[1] This binding is shown in Figure 2. Succinylcholine binds to the presynaptic receptors and causes membrane depolarization and an increase in muscle tension (fasciculations).

If an NDMR is given before the succinylcholine, it will bind to presynaptic nicotinic neuronal acetylcholine receptors and block the binding of succinylcholine; therefore, fasciculations should be reduced or prevented. Figure 3 provides a graphic representation of the blocking actions of the NDMRs on the binding of succinylcholine to presynaptic nicotinic acetylcholine receptors. The 3 NDMRs bind at the presynaptic nerve terminal to block the binding of succinylcholine, thus reducing or preventing fasciculations. The width of the arrows in Figure 3 indicates the relative ability of the NDMRs to prevent fasciculations. The wider the arrow, the more efficient the drug. As mentioned, tubocurarine is the gold standard NDMR for defasciculation. Studies indicate that rocuronium has efficacy for defasciculation.[3,6] To our knowledge, cisatracurium had not been examined for defasciculation before the present study. Anesthesia care providers are constantly searching for an alternative to tubocurarine that has similar effectiveness for defasciculation but that does not produce unwanted side effects.

Methods and materials

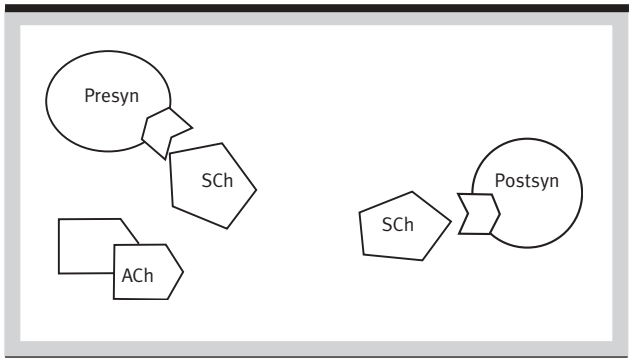
The research design was a prospective, randomized, double-blind, clinical drug comparison. Human clinical investigation committee approval was obtained, and subjects provided written, informed consent. A convenience sample was obtained of adult patients undergoing surgery with general endotracheal anesthesia at a military community hospital.

Figure 1. Normal binding of acetylcholine (ACh) to postsynaptic nicotinic ACh receptors (Postsyn) causing muscle contraction*



*** ACh indicates acetylcholine.**

Figure 2. Succinylcholine (SCh) binds presynaptically (Presyn) and postsynaptically (Postsyn).*

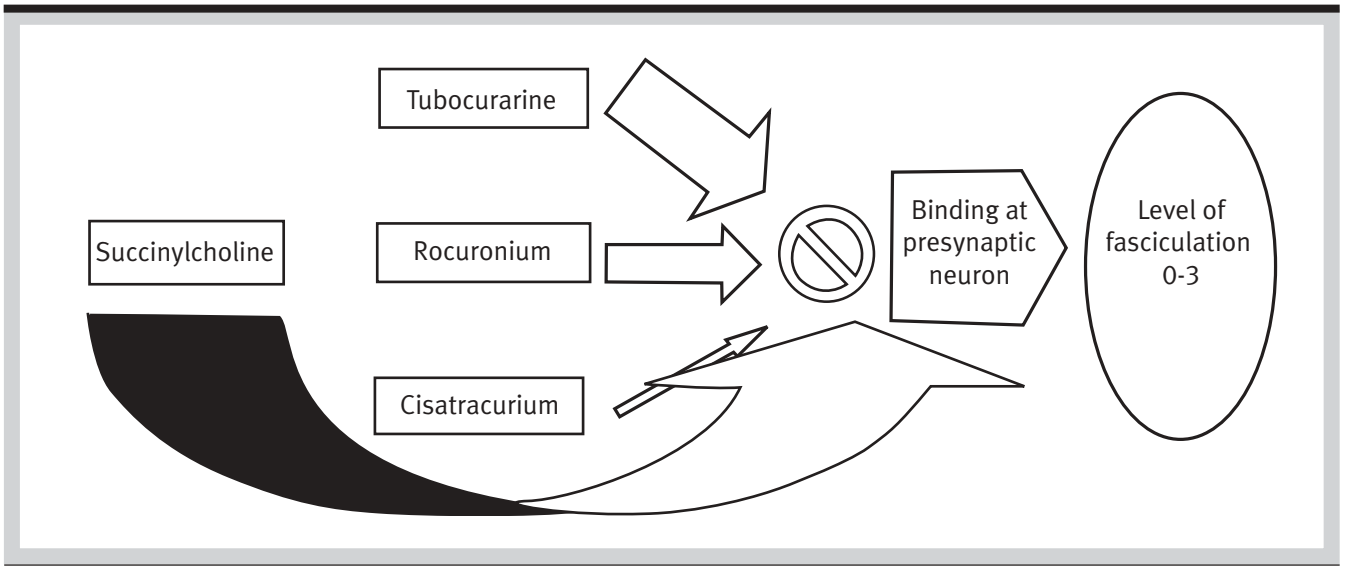


*** ACh indicates acetylcholine.**

For study inclusion, volunteers were English speaking and reading adults undergoing procedures requiring general endotracheal anesthesia in the inpatient or outpatient setting. They were to be designated as ASA physical status I or II without an emergency qualifier.

Exclusion criteria for patient recruitment and selection were consistent with many of the contraindications and relative contraindications associated with succinylcholine. Patients with increased intraocular pressure or increased intracranial pressure were excluded, as succinylcholine-induced muscle fasciculations are associated with further increases in these pressures. Patients with an atypical plasma cholinesterase level, taking trimethaphan or cholinesterase inhibitors (as these may affect the mechanism of action and metabolism of succinylcholine), or with a serum potassium level greater than 5.0 mmol/L (5.0 mEq/L; since succinylcholine has been associated with raising the serum potassium level) were excluded. Patients with a family history of malignant hyperthermia or suspected malignant hyperthermia susceptibility were not approached for the study. Other exclusion criteria included use of medications with muscle relaxant properties such as

Figure 3. Nondepolarizing muscle relaxants (NDMRs) block the action of succinylcholine at presynaptic receptors.*



*** The width of the arrows indicates the proposed relative ability of the NDMRs to prevent fasciculations. The wider the arrow, the more efficient the drug.**

baclofen (which interfere with the manifestation of any potential fasciculations), burn or crush injuries greater than 24 hours old, pregnancy, and age younger than 18 or older than 65 years. Any patient needing a rapid-sequence induction was excluded from the study. Finally, any patient with a history of neuromuscular disease such as Duchenne muscular dystrophy was excluded from study participation. Response to neuromuscular blockers often is unpredictable.

Volunteers were assigned randomly to 1 of 4 groups. Each of the experimental groups received tubocurarine (group 1), rocuronium (group 2), or cisatracurium (group 3) for defasciculation. The control group (group 4) received saline in the place of one of the drugs. The investigator collecting data was blinded to the drug used; however, the staff member who prepared the medication knew what was being administered to ensure patient safety. The efficacy of the pretreatment in preventing or reducing the degree of succinylcholine-induced muscle fasciculations was measured. An investigator observed for the presence and degree of succinylcholine-induced muscle fasciculations after succinylcholine administration and before intubation by using the Harvey Scale.[6] The scale was developed by Harvey et al[6] with 4 point ratings from 0 to 3: 0, no fasciculation; 1, mild, fine fasciculations of the eyes, neck, face, or fingers without limb movement; 2, moderate fasciculations occurring at more than 2 sites or obvious limb movement; 3, vigorous or severe, sustained, and widespread fasciculations. Widespread use of this tool has established its validity and reliability.

Interrater reliability was established before the clinical study by 8 inductions with succinylcholine observed and rated simultaneously by the 3 investigators.

The effect size for this research study was determined from a post hoc calculation of the power achieved in the study by Harvey et al.[6]

A conservative effect size of 1 SD or Cohen f[8] of 1.0 between group means was used to calculate sample size. Sample Power V 1.2 (SPSS, Inc, Chicago, Ill) was used to calculate the required sample size with desired effect size, power, and type I error. Type I error was set at 0.01. Sample size was determined to be 9 subjects per group. To compensate for an anticipated 10% attrition, the sample size was increased to 10 subjects per group. This required enrollment of a total of 40 subjects.

Before beginning the study, 10 cards were made for each experimental group. These cards (termed *drug cards*) listed the drug or control to be used and the dosage. These were paired with a second card, the data card. Each *data card* was marked with the subject number. The data card provided categories and space for the fasciculation scale and recording the fasciculation rating, demographic data, adverse events, and drug (saline) given. Each set of cards was placed in a sealed envelope. The envelopes were shuffled to ensure randomization. The envelopes were then numbered 1 through 40 and placed in a secured box in the anesthesia workroom.

The following procedures were used for data collection:

1. Patients identified in the preanesthetic interviews or before the day of surgery were evaluated for

enrollment. They were informed about the study in their rooms and asked to participate. Consent was obtained before the administration of protocol medication.

2. An investigator took a numbered, sealed envelope from the secured box in the anesthesia workroom and gave it to the staff member assisting the investigator. The staff member opened the envelope and gave the investigator the data card so that demographic data could be recorded.

3. The staff member retained the first data card and prepared the drug (or saline) to be given, as assigned by the drug card, to a standardized volume of 3 mL, out of the sight of the investigator to ensure blinding. The staff member did not grade the fasciculations.

A standardized anesthesia induction protocol was implemented for all participants. First, in the preoperative holding area, a loading dose of lactated Ringer's intravenous fluid, 300 to 500 mL, was administered, followed by the anxiolytic midazolam hydrochloride, 0.025 mg/kg intravenously. The patient then was transported into the operating room. Monitors were applied, and the patient was preoxygenated. Next, tubocurarine, 50 µg/kg; rocuronium, 50 µg/kg; cisatracurium, 20 µg/kg; or a 0.9% solution of sodium chloride (saline), which had been prepared by the staff member to a standardized volume of 3 mL, was given. Response was assessed. Fentanyl, 2 µg/kg, was given intravenously 2 minutes after administration of the assigned study drug or saline. Propofol, 2 mg/kg, was administered 3.5 minutes after administration of the assigned study drug or saline. Mask ventilation was established. Next, succinylcholine, 1.5 mg/kg, was administered intravenously. The presence or absence and degree of fasciculations were observed and evaluated by the investigator. When intubation conditions were present, the subject was intubated. Once tube placement had been confirmed, the airway was secured, and the anesthetic plan was implemented.

As in the study by Harvey et al,[6] a defasciculation dose of rocuronium, 50 µg/kg, was used. A defasciculation dose of 20 µg/kg was used for cisatracurium, which is 10% of the intubating dose, 200 µg/kg.[9]

During maintenance, the investigators recorded their evaluations of the fasciculations according to the 4-point scale on the data card and on the anesthetic record. After the fasciculation rating had been recorded, the staff member informed the investigator of the drug (or saline) used, which then was recorded on the anesthetic record and on the data card.

• *Sample.* The beneficiary population of this community hospital's surgical services is primarily a reflection of the population of the military post on which it is located. This population consists of mostly young, healthy, white men. One subject was eliminated from the study due to a deviation from study protocol. Demographic characteristics are given in Table 1. Table 2 gives the mean (SD) for body temperature, age, height, and weight for groups 1 through 4 and for the entire study sample. Subjects' ages ranged from 18 to 39 years, height from 59 to 72 inches, and weight from 55 to 100 kg. The sample had a gender predominance of males.

The data were analyzed using Statistical Package

Table 1. Frequency table for sex, age, and ASA category*

	Frequency (%)	Cumulative percentage
Sex		
Male	26 (65)	65
Female	14 (35)	100
Total	40 (100)	
Race		
White	29 (72)	72
African American	5 (12)	84
Hispanic	6 (15)	99
Total	40 (100)	
ASA category		
I	16 (40)	40
II	24 (60)	100
Total	40 (100)	

*** Percentages do not all total 100 because of rounding.**

Table 2. Mean (SD) temperature, age, height, and weight for the 4 study groups

	Rocuronium	Tubocurarine	Cisatracurium	Saline	Total
Temperature, °C	36.7 (0.48)	36.5 (0.85)	35.9 (0.74)	36.4 (0.75)	36.4 (0.75)
Age, y	26.4 (6.31)	25.6 (6.40)	27.6 (6.02)	26.4 (6.57)	26.5 (6.12)
Height, in	65.8 (4.39)	69.4 (2.50)	68.3 (3.37)	67.7 (2.50)	67.8 (3.40)
Weight, kg	73.1 (13.1)	75.1 (7.63)	78.7 (11.6)	72.7 (13.05)	79.9 (11.3)

Table 3. Raw data for fasciculation scores*

Fasciculation score	Rocuronium	Tubocurarine	Cisatracurium	Saline*
0	9	8	4	1
1	0	1	0	1
2	1	1	4	2
3	0	0	2	5
Total	10	10	10	9

*** One patient in the saline group was excluded from the study due to a deviation from study protocol.**

for Social Sciences, version 9.0, (SPSS). Cross-tabulation statistics were used to facilitate analysis of demographic statistics.

Results

Data analysis determined that choice of the drug for defasciculation affects the degree and/or incidence of succinylcholine-induced muscle fasciculations (Table 3). The mean fasciculation score (measured on a 0-3 scale) in group 1 was 0.3, and it was 0.2 in group 2. The score was higher in groups 3 and 4, 1.4 and 2.0, respectively. There was no statistically significant difference between saline and cisatracurium or between rocuronium and tubocurarine for defasciculation (Table 4).

Statistically significant differences were demonstrated between the rocuronium and cisatracurium fasciculation scores, the tubocurarine and cisatracurium fasciculation scores, and the tubocurarine and saline fasciculation scores. Table 4 clearly demonstrates the relationships yielded by the study. The H value of 10.176 (P = .001) indicates a significant statistical difference between tubocurarine and saline for defasciculation. The H value is the test statistic for the Kruskal-Wallis analysis of variance (ANOVA), which tests the difference in scores of 3 or more independent groups.[10] The H value of 4.279 (P = .039) also indicates a statistically significant difference between tubocurarine and cisatracurium for defasciculation. The data demonstrated no statistical difference between tubocurarine and rocuronium for defasciculation (H = 0.300; P = .584) compared with saline. We also found a significant statistical difference between rocuronium and cisatracurium with an H value of 5.437 (P = .020).

Table 4. Kruskal-Wallis analysis of defasciculation*

	H value	*P* value
Tubocurarine/saline	10.176	.001
Tubocurarine/rocuronium	0.300	.584
Tubocurarine/cisatracurium	4.279	.039
Cisatracurium/saline	2.393	.122
Rocuronium/saline	11.238	.001
Rocuronium/cisatracurium	5.437	.020

*** There was a strong statistical significance for efficacy as a defasciculating drug between tubocurarine and saline, tubocurarine and cisatracurium, and rocuronium and cisatracurium as indicated by the H and *P* values. The relationship between cisatracurium and saline was not statistically significant. Note the lack of a statistically significant difference between tubocurarine and rocuronium.**

Discussion

To our knowledge, our study is the first to compare rocuronium and tubocurarine with the relatively newer NDMR cisatracurium in the prevention or reduction of succinylcholine-induced muscle fasciculations. Fasciculations are theorized to be caused by occupation of succinylcholine at acetylcholine nicotinic neuronal (presynaptic) receptors at the neuromuscular junction. The research hypothesis that there will be significant differences in the efficacy of tubocurarine, rocuronium, and cisatracurium compared with saline in reducing or preventing succinylcholine-induced muscle fasciculations in ASA physical status I or II patients aged 18 to 65 years and undergoing surgery that required general endotracheal anesthesia was supported partially. Our data establish that rocuronium is as efficacious as tubocurarine for defasciculation. Table 3 demonstrates that 90% (9/10 in each group) of the subjects in groups 1 and 2 experienced no fasciculations or mild fasciculations. Only 40% (4/10) and 22% (2/9), respectively, of groups 3 and 4 experienced no or mild fasciculations.

The findings of our study further support the superior efficacy of rocuronium and tubocurarine for preventing or reducing succinylcholine-induced muscle fasciculations compared with cisatracurium and with

saline. Our study supports the finding of Harvey et al,[6] that rocuronium and tubocurarine are equally efficacious for preventing succinylcholine-induced muscle fasciculations. However, our use of ordinal data and analysis with the Kruskal-Wallis ANOVA yielded more statistically powerful information than the study by Harvey et al.[6] Our data not only address the presence or absence of succinylcholine-induced muscle fasciculations (nominal data), but also the severity of succinylcholine-induced muscle fasciculations. The findings demonstrate that use of cisatracurium for defasciculation is similar to using saline (P = .122). Our conclusion with regard to cisatracurium is that this agent is not effective, at the dose evaluated, for defasciculation.

This study was conducted in a military community hospital. The sample population mirrored the beneficiary population served by this hospital (primarily active duty soldiers). On initial review, the preponderance of males in the study might have been interpreted as a limitation. According to Harvey et al,[6] sex makes no difference with respect to succinylcholine-induced muscle fasciculations. Our study supports that finding.

The demographic characteristics of the individual groups were consistent throughout the sample. The sample included 65% (26/40) men and 35% (14/40) women, with a mean age of 26.5 years. Most subjects were white (29/40 [72%]); the mean height was 67.8 inches and mean weight of 79.9 kg. Our method of randomization was effective. Tables 1 and 2 demonstrate the homogeneity of the groups. Demographic analyses show the results cannot be attributed to variations between treatment groups (P = .304). The internal validity was enhanced by our interrater reliability (Spearman r = 0.89). A strength of our study is that we did not need to rely on staff other than anesthesia staff or agencies to help with data collection or analysis.

Implications for anesthesia nursing include an alternative to tubocurarine when defasciculation is desired. Even though tubocurarine is an inexpensive agent with which most anesthesia providers are familiar, there are instances when all agents associated with histamine release are to be avoided (eg, patients with asthma). Since there are alternatives to tubocurarine for muscle relaxation after intubation, tubocurarine is used rarely other than for defasciculation. If rocuronium is the agent to be used for muscle relaxation after intubation, rocuronium also can be used for defasciculation. The anesthesia care provider then would use only 2 agents (rocuronium and succinylcholine) rather than 3 (tubocurarine, succinylcholine, and rocuronium).

Points for further inquiry include determining the optimal time between dosing for defasciculation and the administration of succinylcholine; determining whether reduced severity of succinylcholine-induced muscle fasciculations correlates with reduced intracranial and intraocular pressures when rocuronium is used for defasciculation; and determining whether a higher dose of cisatracurium would improve its efficacy for defasciculation.

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AUTHORS

CPT Cybil A. True, CRNA, MSN, USA, AN, is an anesthesia provider at Brooke Army Medical Center, Fort Sam Houston, Tex.

CPT Pamela J. Carter CRNA, MSN, USA, AN, is an anesthesia provider at Yongsan Army Garrison, South Korea.

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