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Can Early Administration of Neostigmine, in Single or Repeated Doses, Alter the Course of Neuromuscular Recovery from a Vecuronium-induced Neuromuscular Blockade?

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The authors sought to determine whether neostigmine, given at a time when no response to peripheral nerve stimulation could be elicited, hastened recovery from a vecuronium-induced neuromuscular blockade (NMB). The effect of neostigmine (70 μg/kg) in antagonizing a profound (no-twitch) vecuronium-induced (0.1 mg/kg) NMB in 40 healthy patients was studied. Patients were randomly assigned to one of four groups specifying the sequence of neostigmine administration. Fifteen minutes after the administration of vecuronium, when there was no detectable twitch response, each patient received either neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg) or an equivalent volume of normal saline (placebo). When T1 (the first response in the train-of-four [TOF] sequence) recovered to 10% of control, patients again received either neostigmine with glycopyrrolate in the same doses as before or the placebo. The following variables were measured: times from vecuronium injection until T1 recovered to 10% (t [10]) and 90% (t [90]) of control, and time until the TOF ratio was equal to 75% (t [TOF75]). Mean values of t (90) and t (TOF75) were shorter (54.7–75.2 min and 60.4–79.5 min, respectively) for the three groups who received neostigmine as compared with patients who received two doses of placebo (104.3 and 122.6 min, respectively). There were no differences in the t (90) and t (TOF75) values among the three groups who received neostigmine. The authors concluded that the total time to achieve adequate recovery of neuromuscular function is the same whether neostigmine (70 μg/kg) is administered 15 min after vecuronium (0.1 mg/kg) or whether neostigmine is given when T1 has recovered to 10% of control. Furthermore, a second dose of neostigmine (70 μg/kg) neither hastens nor prolongs recovery. Thus, recovery time from a profound vecuronium-induced NMB can be shortened with the administration of neostigmine given before spontaneous recovery, and repeated administration of neostigmine does not alter the course of recovery. (Key words: Anesthetics, volatile: isoflurane. Antagonist: neostigmine; neuromuscular relaxants. Measurement techniques: neuromuscular blockade. Neuromuscular relaxants: vecuronium.)

IN CLINICAL PRACTICE, the anesthesiologist may be faced with the problem of antagonizing a neuromuscular blockade (NMB) when there is no muscle response to stimulation of the ulnar nerve. The rate of recovery of neuromuscular function is related to the percent of recovery at the time reversal is administered; this has been demonstrated for many of the nondepolarizing muscle relaxants.[1–4] It is unclear, however, whether administration of an antagonist before any evidence of spontaneous recovery results in an altered recovery time. Caldwell *et al.*[5] showed that a vecuronium-induced NMB can *not* be rapidly antagonized by neostigmine when given 5 min after the onset of NMB (recovery took >40 min). At the other extreme, several investigators showed that NMB can be rapidly reversed if neostigmine is given when control twitch tension has returned to 10% or greater.[6–9]

No study has examined the period between 5 and 40 min after onset of NMB. This has practical application because surgical requirements for muscle relaxation can suddenly change, leaving the anesthesiologist in the awkward position of needing to rapidly reverse the NMB soon after a dose of muscle relaxant has been given. We therefore sought to compare neostigmine antagonism at two levels of NMB: the first occurring at a pre-specified time after vecuronium administration (resembling the clinical situation of the conclusion of surgery and no detectable muscle twitch) and at 10% recovery of control twitch tension. Our aim was to determine whether neostigmine given before evidence of spontaneous recovery could adequately antagonize a profound vecuronium-induced NMB and to determine if giving a second dose of neostigmine had any effect on the rate of recovery of neuromuscular function.

Materials and Methods

After approval from our institution's Committee on Human Research, written informed consent was obtained from 40 ASA Physical Status I or II patients who were aged 18–64 yr and who presented for elective surgery. Patients were excluded from the study if evidence of renal, hepatic, cardiovascular, or neuromuscular disease existed.

Preanesthetic medication consisted of midazolam (0.02–0.05 mg/kg iv); anesthesia was induced with thiopental (2–7 mg/kg iv) or isoflurane (1–3%) inspired concentration. Tracheal intubation was accomplished without neuromuscular blocking drugs. Following endotracheal intubation, anesthesia was maintained with isoflurane (0.7–0.9%) and 60% N_2O (end-tidal concentration as measured by mass spectrometry). Fentanyl (1–5 μg/kg iv) was given as needed to ensure adequate anesthetic depth and hemodynamic stability. Ventilation was controlled to maintain end-tidal P_{CO_2} at 35–40 mmHg. Esophageal temperature was maintained at 36°–37.5° C by surface warming. A Grass (Grass Medical Instruments, Quincy, MA) S88 nerve stimulator delivered supramax-

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imal, square-wave impulses of 0.2-msec duration in a train-of-four (TOF) sequence (2 Hz) *via* 27-G needles placed subcutaneously near the ulnar nerve at the wrist. Trains of stimuli were repeated at intervals of 15 s, and the evoked mechanical response of the adductor pollicis muscle was measured by a force-displacement transducer (Professional Instruments® APM-X) and displayed on a polygraph. When the amplitude of the first twitch response of each train-of-four (T1) reached a plateau and stabilized, it was used as the control to which all subsequent responses were compared.

Twenty minutes after stable anesthetic conditions and baseline neuromuscular measurements were recorded, each patient received an iv bolus of vecuronium (0.1 mg/kg). Fifteen minutes after receiving vecuronium (and when no twitch response was detectable), patients were given drug 1: either normal saline (placebo) or neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg), depending on their group assignment. When the amplitude of the first twitch in the TOF sequence (T1) had recovered to 10% of control, patients received drug 2: either placebo or neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg; fig. 1, Experimental design).

Patients were randomly assigned to one of four study groups (10 patients per group) as follows.

Group 1. Placebo/Placebo (PP). Patients received the placebo (normal saline, iv bolus) 15 min after vecuronium (0.1 mg/kg, iv bolus) and again when T1 recovered to 10% of control. This group received no neostigmine and thus served as the control group.

Group 2. Placebo/Neostigmine (PN). These patients received the placebo 15 min after receiving vecuronium and neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg, iv bolus) when T1 recovered to 10% of control.

Group 3. Neostigmine/Placebo (NP). This group received neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg) 15 min after vecuronium and the placebo when T1 recovered to 10% of control.

Group 4. Neostigmine/Neostigmine (NN). Patients in this group received neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg) 15 min after receiving vecuronium (0.1 mg/kg) and again when T1 recovered to 10% of control.

The following recovery variables were recorded: t (10) = time from vecuronium injection until T1 had returned to 10% of control; t (90) = time from vecuronium injection until T1 returned to 90% of control; t (10–90% [recovery rate]) = time from 10–90% recovery; t (TOF75) = time from vecuronium injection until TOF ratio was equal to 75%.

Means and standard deviation were calculated for each group and recovery time (table 1). Differences between mean recovery times for each recovery variable were analyzed for each group by one way analysis of variance. Paired comparisons were then made for each group and recovery variable using Student-Newman-Keuls test for multiple comparisons (table 2). Differences were considered significant at $P < 0.05$. Power analysis indicated that the number of patients studied was sufficient to detect a 20% change in mean recovery times.[10]

Results

The four groups of patients did not differ significantly with respect to age, body weight, or gender. Their mean age and body weight were 34.5 ± 11.6 (SD) yr and 75.1 ± 14.4 (SD) kg.

All three groups receiving neostigmine (PN, NP, NN) had shorter times to recovery (t [90], 54.7–75.2 min; t [TOF75], 60.4–79.5) than the PP group who received two doses of placebo (t [90], 104.3 min; t [TOF75], 122.6 min; table 1 and fig. 2). The group with the longest recovery times for t (90) and t (TOF75) was PP (fig. 2). No

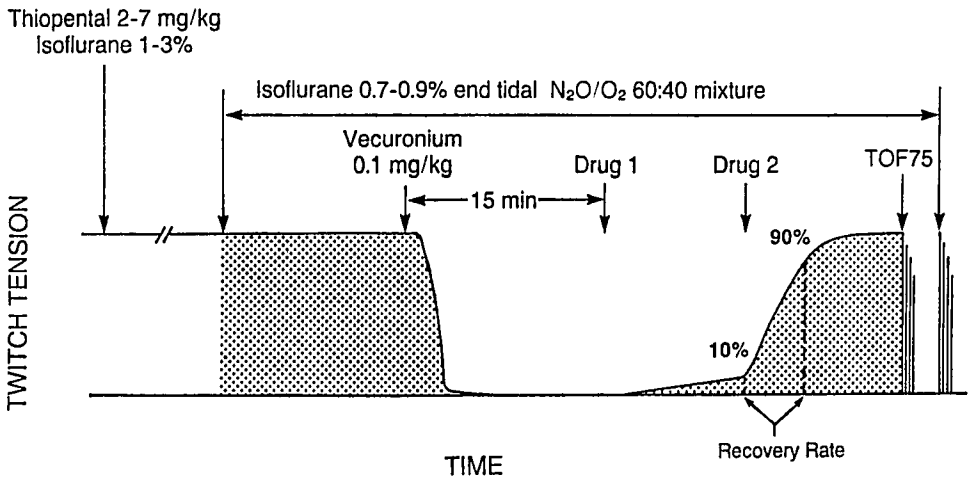

FIG. 1. Experimental design: twitch tension *versus* time. Twenty minutes after stable anesthetic conditions and baseline neuromuscular measurements, each patient received vecuronium 0.1 mg/kg iv bolus. Fifteen minutes after receiving vecuronium, patients were given drug 1, which was either normal saline (placebo) or neostigmine 70 μg/kg with glycopyrrolate 15 μg/kg, depending on their group assignment. When the amplitude of the first twitch in the train-of-four sequence had recovered to 10% of control twitch, patients received drug 2, which was either placebo or neostigmine (70 μg/kg) with glycopyrrolate (15 μg/kg).

TABLE 1. Mean Recovery Times by Group

Group	n	t(10)	t(90)	t(10–90%)	t(TOF75)
Placebo/placebo	10	41.3 (11.8) [22–48]	104.3 (28.1) [52–148.8]	62.61 (19.3) [29.6–87]	122.6 (39.4) [69.6–207]
Placebo/neo	10	44.4 (21.31) [16.8–86.6]	54.7 (22.7) [29–104]	10.4 (7.8) [1.8–27]	60.4 (21.8) [37–104.6]
Neo/placebo	10	21.4 (4.8) [16–29.6]	75.2 (22) [41.4–112.8]	54.7 (19.4) [25.4–83.2]	79.5 (24.7) [44–119.4]
Neo/neo	10	22 (5.6) [16–31.6]	72 (37.3) [18.8–110.8]	48.6 (35.7) [2.8–115.4]	71.5 (32.5) [23.5–103.4]

Values shown are mean, SD (in parentheses), and range (in brackets).
Recovery variables: t(10) = time from administration of vecuronium to 10% recovery of control twitch tension; t(90) = time from administration of vecuronium to 90% recovery of control twitch tension; t(10–90%) = time from recovery of 10–90% of control twitch tension; t(TOF75) = time to achieving for ratio of 75% fourth to first twitch in the train-of-four stimulation.

significant differences were found among the groups who received neostigmine for recovery to t (90) or to recovery of t (TOF75; table 2).

The NP and NN groups reached t (10) more rapidly (21.4 and 22 min *vs.* 41.3 and 44.4 min, respectively) than the groups that did not receive neostigmine before evidence of spontaneous recovery (fig. 2). There were no differences in recovery between the NN and NP groups.

The PN group had the most rapid recovery rate from 10–90% (fig. 3). The slope of the recovery rate (10–90%) for the PP group was similar to the NP and the NN groups but occurred at a later time.

Discussion

The principal finding of this study was that there were no differences in recovery among the three groups of patients who received neostigmine. We demonstrated that, under the conditions of our study, the time from t (10–90) is not shortened by early administration of neostigmine; thus, recovery to t (90) or (TOF75) is the same for all three groups regardless of when neostigmine is given or whether a second dose is given.

This study addressed the clinical problem of antagonizing a profound NMB. We defined a profound NMB as one that yields an undetectable response from TOF stimulation of the ulnar nerve. Our study design was chosen to determine which of several clinical options results in the most rapid and reliable antagonism from a vecuronium-induced NMB. Previous investigators examined the effects of neostigmine antagonism once recovery had begun to occur[1–4,6–9,11] or in the time period immediately after vecuronium administration.[5] None of these represent the clinical situation our study attempted to address. We chose to give neostigmine 15 min after vecuronium administration because it represents a clinically relevant time period during NMB: when no evidence of recovery has occurred, but sufficiently after the initial muscle relaxant administration, thereby simulating the common problem of a profound NMB at the conclusion of surgery. Although this model may not represent the same block

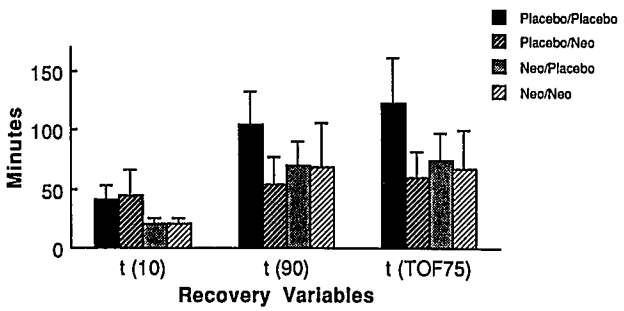

FIG. 2. Group comparison: times to recovery. Recovery from neuromuscular blockade as a function of time from administration of vecuronium by treatment group. All results are mean (±SD) times to recovery as a percentage of control muscle twitch t(10) is the time from vecuronium administration to 10% recovery of control twitch tension; t(90) is the time from administration of vecuronium to 90% recovery of control twitch tension; and t(TOF75) is the time from administration of vecuronium to achieving a ratio of 75% of the last twitch to the first twitch in the train-of-four.

TABLE 2. Multiple Comparisons by Group for Each Recovery Variable

Group Comparison	Statistical Significance by Recovery Variables			
	t(10)	t(90)	t(10–90%)	t(TOF750)
PP *vs.* PN	NS	<0.05	<0.05	<0.05
PP *vs.* NP	<0.05	<0.05	NS	<0.05
PP *vs.* NN	<0.05	<0.05	NS	<0.05
PN *vs.* NP	<0.05	NS	<0.05	NS
PN *vs.* NN	<0.05	NS	<0.05	NS
NP *vs.* NN	NS	NS	NS	NS

Statistical significance was defined as $P < 0.05$. P values for each group comparison were calculated with the Student-Newman-Keuls test for multiple comparisons.

PP = placebo/placebo; PN = placebo/neostigmine; NP = neostigmine/placebo; NN = neostigmine/neostigmine.

Recovery variables: t(10) = time from administration of vecuronium to 10% recovery of control twitch tension; t(90) = time from administration of vecuronium to 90% recovery of control twitch tension; t(10–90%) = time from recovery of 10–90% of control twitch tension; t(TOF75) = time to achieving ratio of 75% for fourth to first twitch in the train-of-four stimulation.

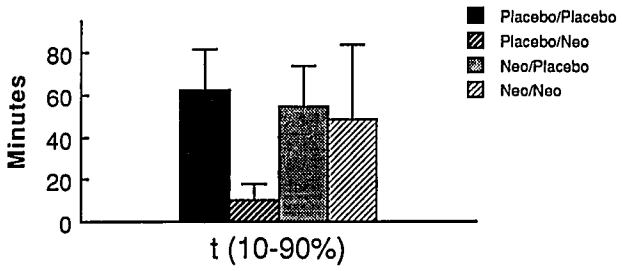

FIG. 3. Recovery rate 10–90%. Recovery from neuromuscular blockade as a function of time from 10 to 90% of control twitch. Results are mean ± SD for each group.

that results from multiple doses given during a long anesthetic, it allows comparisons of neostigmine antagonism at two levels of recovery under standard anesthetic conditions.

We assessed the level of NMB following vecuronium administration by measuring the response to TOF stimulation. We chose to monitor TOF ratio and not posttetanic count[12,13] because of the effect of tetanus on the neuromuscular junction. Tetanic stimulation causes an increase in synthesis and mobilization of acetylcholine that persists for several minutes and modifies the response to TOF stimulation.[14] Therefore, we did not attempt to quantify the level of NMB following vecuronium administration until recovery of TOF responses occurred. Because patients were assigned to study groups randomly, however, the level of recovery of patients in the groups 15 min after vecuronium administration should be comparable.

In an earlier study, Caldwell *et al.*[5] measured recovery in patients who had received either atracurium or vecuronium and reported mean recovery times from vecuronium to TOF70 of 43.5 and 66.7 min in patients who received neostigmine (70 μg/kg) and no antagonist, respectively. In the current study, our mean recovery time to TOF75 was 60.4–79.5 min in patients receiving neostigmine. Our longer recovery times may be explained by several factors: 1) different starting points for measuring recovery were used (Caldwell measured time from 5 min after establishing vecuronium NMB to recovery, and we measured time from administration of vecuronium to recovery); 2) end-points of recovery were different (TOF70 *vs.* TOF75); and 3) different inhaled anesthetics were used (halothane *vs.* isoflurane; Rupp *et al.* demonstrated that isoflurane augments a vecuronium-induced NMB more than halothane[15]).

Our data are consistent with Caldwell *et al.*[5] in that neostigmine does not rapidly antagonize a profound NMB as neither study demonstrated recovery in less than 40 min. Also of note is that our data represent antagonism in the presence of relatively high concentrations of isoflurane. In the clinical setting of attempting antagonism at the end of surgery, recovery is likely to be more rapid because of the decreasing concentration of isoflurane. However, stable isoflurane concentration was necessary for the purposes of this study to adequately control for the effect of isoflurane on neuromuscular transmission.

Neostigmine itself can cause a depolarizing NMB. Payne *et al.* found that patients who were anesthetized with nitrous oxide/narcotics and who had received no muscle relaxants had a reduction in their peak tetanic contraction and a severe fade when given neostigmine.[16] These effects lasted 20 min after one and two doses of neostigmine (2.5 mg each). In our study, the group that received two doses of neostigmine (NN) showed no evidence of depressed neuromuscular function or prolongation of recovery; however, this may be explained by the different modes of detecting recovery (TOF *vs.* tetanic stimulation). If neostigmine potentiates an NMB, we were unable to demonstrate such an effect by our methodology.

Alternatively, recovery may be hastened if small doses of neostigmine are given before a larger dose as in a priming effect.[17,18] Comparisons with these studies and the current one are at best speculative since different doses of neostigmine (50 *vs.* 70 μg/kg) and different muscle relaxants (atracurium *vs.* vecuronium) were used. Also, the time interval between the two doses in our study was approximately 4–6 min rather than the 1–3 min time interval that Naguib and Abdulatif found to be optimal in accelerating recovery. In addition, these studies attempted initial antagonism at 10% twitch recovery. Most recently, Donati *et al.* found that there was no difference in response to single twitch or TOF stimulation in patients given single *versus* priming doses of neostigmine to reverse an atracurium NMB at 1% twitch height recovery.[19] Our results are similar because we found no evidence of a hastened recovery in the NN group. In fact, the NN and NP group had similar recovery patterns (fig. 4), and it appears that the second dose of neostigmine had no effect on the neuromuscular junction. We speculate that this lack of effect was because the initial dose of neostigmine had produced maximal inhibition of the acetylcholinesterase; therefore, further inhibition by the second dose of neostigmine was not possible. Our results are consistent with those of Jones *et al.* who gave patients two doses of neostigmine of 2.5 mg/kg to antagonize a 50% and 90% NMB. These authors also found no effect on neuromuscular recovery following the second dose of neostigmine.[20]

In summary, we showed that time from vecuronium injection to TOF75 is the same regardless of when antagonism is attempted. Nonetheless, there does not appear to be any advantage in giving neostigmine before the onset of spontaneous recovery. Indeed, there may be disadvantages since the predicted response for individual patients is quite variable. The advantage of giving neostigmine after beginning spontaneous recovery is the facilitation of measurement of a more readily observed response. There appears to be no benefit in administering repeated

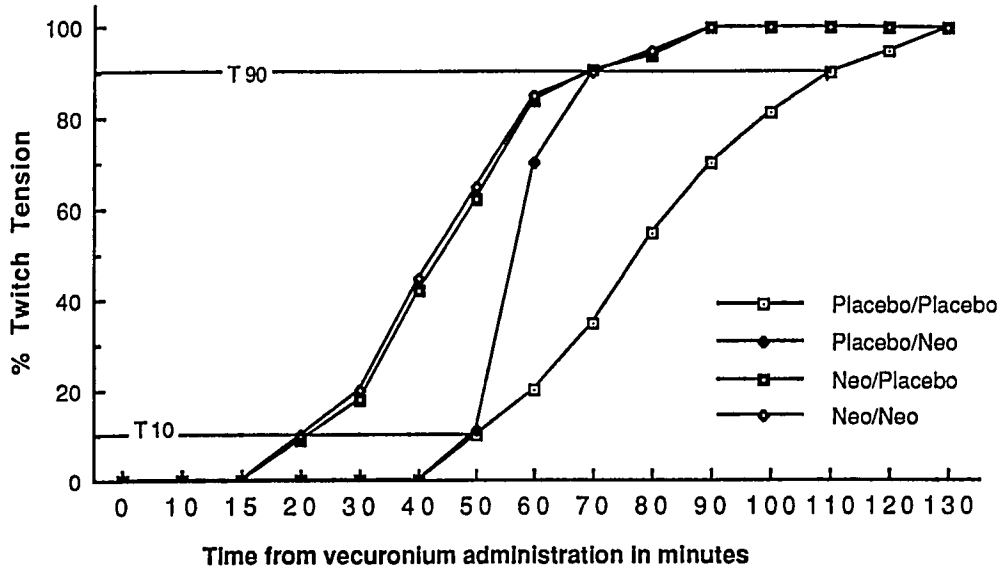

FIG. 4. Group comparison: recovery patterns for each group. Twitch tension is correlated with time after vecuronium administration. Note that although their initial recovery rates were different, all neostigmine groups had recovered completely at similar times, unlike placebo (*i.e.*, all neostigmine groups reached t(90) at similar times). However, the recovery pattern differed among the four groups. The most rapid response was seen in the placebo/neo group, in which spontaneous recovery occurred to 10% of control twitch tension prior to administration of neostigmine. The curves for the neo/placebo and neo/neo groups are similar to the placebo/placebo curve but shifted to the left, implying that neostigmine has an initial effect and then further recovery parallels spontaneous recovery. Further, the recovery patterns for the groups that received neostigmine prior to spontaneous recovery (neo/placebo, neo/neo) were indistinguishable from each other, suggesting that the second dose of neostigmine had no apparent effect on recovery.

doses of neostigmine in the presence of a profound vecuronium-induced NMB.

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References

1. Katz RL: Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. ANESTHESIOLOGY 28:327–336, 1967
2. Miller RD, Larson CP Jr, Way WL: Comparative antagonism of d-tubocurarine-, gallamine-, and pancuronium-induced neuromuscular blockades by neostigmine. ANESTHESIOLOGY 65: 572–578, 1986
3. Katz RL: Clinical neuromuscular pharmacology of pancuronium. ANESTHESIOLOGY 34:550–556, 1971
4. Kopman AF: Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. ANESTHESIOLOGY 65:572–578, 1986
5. Caldwell JE, Robertson EN, Baird, WLM: Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: Comparison of neostigmine with edrophonium. Br J Anaesth 58:1285–1289, 1986
6. Cronnelly R, Morris RB: Antagonism of neuromuscular blockade. Br J Anaesth 54:183–194, 1982
7. Gencarelli PJ, Miller RD: Antagonism of ORG NC45 (vecuronium) and pancuronium neuromuscular blockade by neostigmine. Br J Anaesth 54:53–56, 1982
8. Mirakhur RK, Gibson FM, Lavery GG: Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. Br J Anaesth 59:473–477, 1987
9. Rupp SM, McChristian JW, Miller RD, Taboada JA, Cronnelly R: Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium, or vecuronium. ANESTHESIOLOGY 64:711–717, 1986
10. Cohen J: Statistical Power Analysis for the Behavioral Sciences. New York, Academic Press, 1977
11. Caldwell JE, Robertson EN, Baird WLM: Antagonism of vecuronium and atracurium: Comparison of neostigmine and edrophonium administered at 5% twitch height recovery. Br J Anaesth 59:478–481, 1987
12. Viby-Mogensen J: Clinical assessment of neuromuscular transmission. Br J Anaesth 54:209–223, 1982
13. Bonsu AK, Viby-Mogensen J, Fernando PUE Fernando, Muchal K, Tamilarasan A, Lambourne A: Relationship of post-tetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. Br J Anaesth 59:1089–1092, 1987
14. Magleby KL: The effect of tetanus and post-tetanic potentiation on facilitation of transmitter release at the frog neuromuscular junction. J Physiol (Lond) 234:327–352, 1973
15. Rupp SM, Miller RD, Gencarelli PJ: Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. ANESTHESIOLOGY 60:102–105, 1984
16. Payne JP, Hughes R, Al Azawi S: Neuromuscular blockade by neostigmine in anaesthetized man. Br J Anaesth 52:69–75, 1980
17. Naguib M, Abdulatif M: Priming with anti-cholinesterases: The effect of different combinations of anti-cholinesterases and priming intervals. Can Anaesth Soc J 35:47–52, 1988
18. Abdulatif M, Naguib M: Accelerated reversal of atracurium blockade with divided doses of neostigmine. Can Anaesth Soc J 33:723–728, 1986
19. Donati F, Smith CE, Bevan DR: "Priming" with neostigmine: Failure to accelerate reversal of single twitch and train-of-four responses. Can J Anaesth 36:30–34, 1989
20. Jones JE, Hunter JM, Utting JE: Use of neostigmine in the antagonism of residual neuromuscular blockade produced by vecuronium. Br J Anaesth 59:1454–1458, 1987