A Prospective Randomized Comparison of Train-of-Four Monitoring and Clinical Assessment During Continuous ICU Cisatracurium Paralysis*

Michael H. Baumann, MD, FCCP; B. Wayne McAlpin, MD; Keith Brown, RN; Praful Patel, MD; Intiaz Ahmad, MD; Robert Stewart, MD; and Marcy Petrini, PhD, FCCP

Study purpose: Train-of-four (TOF) monitoring is often recommended during the continuous use of neuromuscular blockade (NMB) [paralysis] in the ICU. Prior study results are conflicting regarding the benefits of TOF monitoring.

Design: Thirty patients in the medical ICU were randomized to TOF monitoring (n = 16) or to clinical assessment (n = 14) during continuous cisatracurium infusion. TOF monitoring was done at least every 4 h, with the goal being maintenance of one to two twitches. Statistical analysis was performed by two-tailed, unpaired t test (with Bonferroni correction for multiple comparisons), χ², and Fisher exact test, with p < 0.05 considered significant. Given a power of 80%, and the variance seen in the two groups, we estimate that the sample size used is sufficient to detect a change of ≥ 60 min between groups for recovery time.

Results: The mean recovery time after cessation of paralytics was no different between TOF and clinical assessment (45 ± 7 min vs 38 ± 10 min, respectively [mean ± SEM]). No differences were noted for mean APACHE (acute physiology and chronic health evaluation) II entry scores, glomerular filtration rates, or use of corticosteroids. No significant differences were noted between TOF monitoring and clinical assessment in mean total paralysis time (4,118 ± 1,012 min vs 3,188 ± 705 min, respectively), mean total cisatracurium dose (920 ± 325 mg vs 715 ± 167 mg), or dosage (2.3 ± 0.2 μg/kg/min vs 2.9 ± 0.2 μg/kg/min).

Conclusions: TOF monitoring does not lead to improved recovery time or lower cisatracurium dosing compared with monitoring by clinical assessment. We conclude that TOF monitoring is unnecessary, and careful titration of the neuromuscular blocking agent by clinical assessment alone is sufficient in patients undergoing continuous cisatracurium NMB.

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Key words: intensive care; monitoring; neuromuscular blockade; paralysis; train-of-four

Abbreviations: APACHE = acute physiology and chronic health evaluation; AQMS = acute quadriplegic myopathy syndrome; MICU = medical ICU; NMB = neuromuscular blockade; TOF = train-of-four

Neuromuscular blockade (NMB) has been utilized frequently in the past in the intensive care setting in the United States, and may lead to prolonged paralysis. No comprehensive survey of current US use of NMB in an ICU setting appears available. Facilitation of mechanical ventilation, management of intracranial pressure, treatment of muscle spasm, and limiting oxygen consumption

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Correspondence to: Michael H. Baumann, MD, FCCP, 2500 North State St, Division of Pulmonary and Critical Care Medicine, University of Mississippi Medical Center, Jackson, MS 39216-4505; e-mail: mbaumann@medicine.umsmed.edu
However, conflicting results from the few trials have been described. One study noted faster recovery time after paralysis with vecuronium and lower doses of vecuronium using TOF monitoring. TOF monitoring with vecuronium may provide pharmacoeconomic benefits. In contrast, TOF monitoring has not been clearly beneficial in two studies; one study assessed cisatracurium and vecuronium, and the other study assessed cisatracurium. This lack of proven efficacy may be due to inadequate frequency of monitoring, use of different NMB agents, differences in the patient populations, or adequacy of training of the nursing personnel utilizing TOF monitoring.

To help clarify this issue, we randomized patients in the medical ICU (MICU) at the University of Mississippi Medical Center to monitoring by TOF or clinical assessment. Our primary aims were to discover if TOF monitoring compared with clinical assessment during cisatracurium paralysis reduced the incidence of pharmacologic overdose, reduced clinically significant neuromuscular weakness, or allowed use of less cisatracurium to achieve clinical end points.

**Materials and Methods**

**Patient Enrollment**

All patients aged ≥ 18 years and admitted to the University of Mississippi Medical Center MICU who received continuous infusion NMB with cisatracurium (from December 1997 to September 1999) were enrolled in the study. Patients receiving a one-time bolus of cisatracurium or intermittent bolus therapy were not eligible.

Patients may have been started on NMB for up to 4 h (specifically with cisatracurium) outside of the MICU setting (i.e., emergency department, surgical ICU, etc.) and be considered for enrollment. Patients were randomized to either receive TOF monitoring or clinical assessment. The patient’s hospital number was used to choose rows and columns from a random number table. If the number derived from the random number table was an odd number, the patient was assigned to the clinical assessment group; if the number was an even number, the patient was assigned to the TOF group. Demographic information at MICU randomization included the following: age, weight, APACHE score, gender, associated medical/surgical illnesses, and medications.

All patients requiring NMB in the MICU received cisatracurium by MICU protocol that excluded patients with allergies, pregnancy, personal or family history of malignant hyperthermia, a history of significant neuromuscular disease, or major burns currently or within the last 2 years. Nursing training in the use of the TOF monitors and the clinical assessment protocol was held prior to the commencement of the study and frequently during the study to ensure uniformity of care of each patient-enrollment arm.

**NMB Dosing**

All patients received 0.10 mg/kg of cisatracurium as an initial IV loading dose, with a continuous infusion started immediately at an infusion rate of 0.15 mg/kg/h (150 µg/kg/h). The level of NMB was monitored by one of two methods: clinical assessment or TOF every 4 h, with the level of cisatracurium infusion adjusted accordingly. Physician blinding was not performed.

**TOF Application Device**

TOF monitors (Innervator; Fisher & Paykel; Auckland, New Zealand) applied a TOF stimulus through cutaneous self-adherent ECG electrodes affixed to the skin overlaying the distal ulnar nerve. Prior to application of NMB, a supramaximal stimulus level was determined. The adductor pollicis twitch response was monitored. The response to the adductor pollicis muscle was assessed by feeling the patient’s thumb movement (tactile, not visual assessment) after ulnar stimulation. In the event that the adductor pollicis could not be used because of bilateral arm edema or an arterial line placement, the orbicularis oculi was monitored by facial nerve stimulation. All patients regardless of their enrollment group had their level of supramaximal stimulus assessed and electrodes left in place (see assessment of recovery, below).

**TOF Monitoring of NMB**

In those patients undergoing TOF monitoring, the TOF testing occurred every 5 min for the first 30 min after the initial bolus dose (and any subsequent bolus). The level of NMB was then tested every 30 min thereafter, until steady state was achieved. The infusion rate of cisatracurium (including possible additional bolus dosing) was adjusted to maintain one or two twitches until stability (steady state) was noted on two sequential 30-min assessments (may include the first 30-min test after the initial bolus). Once a steady-state infusion rate maintaining one or two twitches was achieved, TOF monitoring occurred at a minimum of every 4 h. At those time intervals, if infusion rates needed adjustment, TOF monitoring occurred every 30 min until a steady-state infusion rate was found (as above).

**Clinical Assessment of NMB**

Clinical assessment of NMB dosing consisted of adjusting the level of blockade based on the observed responses of the patient to NMB. The parameters (responses) followed depended on the need for NMB. Historically, NMB in our MICU setting is most often utilized to achieve patient-ventilator synchrony. Nursing personnel monitored patients with potential patient-ventilator dysynchrony for signs of “buckling,” including elevated mechanical ventilation peak pressures, and adjusted the dose of cisatracurium to eliminate the dysynchrony. Elevated peak pressures, occurring in the face of visible patient-ventilator dysynchrony, were defined as pressures > 40 mm of water pressure (or above the steady-state peak pressures appropriate for lung compliance) persisting despite patient sedation and/or appropriate physician-directed ventilator adjustments. After these adjustments and continued frequent intermittent peak pressures greater than steady state, nursing personnel titrated NMB by protocol to facilitate patient-ventilator synchrony and to establish the steady state.
state or a lower peak pressure. Total absence of patient initiated breaths was not a goal of clinical assessment in patients paralyzed for patient-ventilator dysynchrony except in patients undergoing inverse-ratio (inverse inspiratory/expiratory ratio) mechanical ventilation. Similarly, patients paralyzed due to dangerous motor activity (despite sedation efforts), such as attempted self-extubation, were monitored for such continued dangerous activity, and the paralytic was adjusted accordingly.

Sedation and Pain Relief Measures

A sedative agent (midazolam or lorazepam) was used by protocol in all patients entered into the study. Pain relief agents were limited to morphine sulfate and fentanyl by protocol and were used for all patients.

Assessment of Recovery From NMB

The termination of NMB was at the discretion of the clinician caring for the patient. Once NMB was no longer believed necessary, cisatracurium was terminated and the time noted. Total paralysis time was defined as the time from first inception of NMB to the point that the cisatracurium was terminated.

All patients, regardless of original enrollment group, had a TOF monitor placed immediately before the termination of NMB to determine the level of NMB (baseline recovery level). After NMB was stopped, TOF was measured every 30 min for the next 3 h until four twitches returned, realizing this may not immediately indicate complete absence of neuromuscular receptor blockade.8,9 Plans for prolonged monitoring were included in the study design but were not needed. Our definitions of prolonged paralysis and acute myopathy were not needed due to the prompt recovery of neuromuscular function in the clinical assessment and TOF patient groups. However, prolonged paralysis was defined as having occurred if a patient did not have recovery of four twitches by TOF assessment within 3 h of discontinuation of the cisatracurium infusion. This was based on multiplying the clearance half-life of cisatracurium (approximately 20 to 30 min) by five.10 We adopted 180 min to be conservative in our definition of prolonged paralysis. Acute myopathy was defined by the clinical assessment of a consulting neurologist and the presence of electromyographic and/or muscle biopsy findings compatible with postparalytic myopathy.

Consent

Consent was waived after careful review by our institutional review board. Cited was the fact that the study was evaluating two standard techniques both being used in our institution prior to implementation of the study. Further, the waiver of consent was believed not to place the patient at any risk, and allowed urgent care to be administered without delay.

Statistical and Power Analysis

A power analysis11 was performed with the following assumptions: (1) two groups (clinical assessment and TOF); (2) unpaired t test (significance at p < 0.05); (3) difference considered clinically important: 50% decrease in time (in minutes) to > 70% neuromuscular recovery (TOF with four “twitches”) after cisatracurium infusion was stopped; (4) SD measurement: 85% (based on data by Prielipp et al.8 with 85% being the coefficient of variation—the SD divided by the mean and represented as a percentage); and (5) power of 80%. Initial power analysis yielded a required sample size of 47 in each group (total of 94). However, the high SD seen in the study by Prielipp et al.8 is responsible for the relatively larger samples size required. An interval power analysis was performed by our study statistician (M.P.) after 10 patients in each group were tested, utilizing the SD of each 10-patient group. SD (vs the SEM) is used by convention for our power analysis calculations.12 This determined that 15 patients in each study arm would be adequate. A post hoc power analysis using the SDs of the final study group was performed to determine the size of postparalytic recovery time difference (between the two groups) that the final study group sizes would be sufficient to detect.

Comparisons between groups were made, as appropriate, using an unpaired t test (with Bonferroni correction for multiple comparisons), χ² analysis, or Fisher exact test (p < 0.05 being significant). Given that we are reporting the mean of our study population, the SEM is utilized in lieu of the SD for our data presentation tables.

Results

Patient enrollment is shown in Figure 1. Cisatracurium was the paralytic of choice in our MICU during the study period.

Patient demographics are summarized in Table 1. Considerable overlap in underlying initial diagnoses existed between the two groups, with no difference noted between pulmonary and nonpulmonary diagnoses or between APACHE II scores. Primary pulmonary diagnoses in the TOF group included ARDS (two patients), COPD (two patients), pneumonia (one patient), pulmonary embolus (one patient), and unspecified respiratory failure in a Downs patient; pulmonary diagnoses in the clinical assessment group included pneumonia (three patients), ARDS (one patient), asthma (two patients), and pulmonary embolus (one patient). Nonpulmonary primary diagnoses in the TOF group included bone marrow transplantation (three patients), sepsis (two patients), congestive heart failure (one patient), and leukemia (one patient); nonpulmonary diagnoses in the clinical assessment group included leukemia (two patients), sepsis (one patient), meningitis (one patient), HIV (one patient), congestive heart failure (one patient), and thrombotic thrombocytopenia purpura (one patient). All patients enrolled had their cisatracurium NMB started in the MICU for ventilator dysynchrony. All TOF monitoring was accomplished using the adductor pollicis muscle. No difference regarding administered medications was noted in either the total number of medications received in each group or by medication types (corticosteroid, aminoglycoside, or clindamycin) in each group.

The TOF and clinical assessment groups demonstrated no outcome differences including postparalytic mean recovery times, mean total time paralyzed before discontinuation of paralysis, various measures of total cisatracurium dose or in episodes of prolonged paralysis (Table 2). No documented episodes
of prolonged paralysis syndrome or clinical evidence of acute myopathy were noted. Given a power of 80%, \( p < 0.05 \), and the variance seen in the two groups in the current study, we are able to estimate that our final sample size is sufficient to detect a change \( \geq 60 \) min between groups for postparalysis recovery time.

**DISCUSSION**

The use of NMB to improve ventilator synchrony remains necessary in some patients despite aggressive sedation.\(^1\) Unfortunately, the use of NMB has not come without a price. The occurrence of prolonged paralysis from overdosage of parent drug or active metabolites has been reported with greater frequency since the early 1990s.\(^2\) Various strategies to avoid this complication have been suggested including the use of TOF NMB monitoring.\(^3,12\) A 1995 consensus panel recommended peripheral nerve stimulation to “guide sustained neuromuscular blockade in the ICUs” despite a lack of adequate scientific evidence.\(^13\) This expert opinion (level 3 evidence) recommendation may have been driven by the misperception that TOF success noted in the surgical anesthesia environment can be expected in the ICU setting. A update of this 1995 statement recommends that both clinical assessment and TOF monitoring should be used to adjust the degree of NMB (grade B recommendation), however, noting “more clinical studies are necessary to determine the best techniques.”\(^3\)

We carefully looked for prolonged paralysis in this patient cohort utilizing frequent postparalytic TOF testing and for acute myopathy using close clinical assessment. Acute myopathy associated with NMB appears distinct from the critical care polyneuropathy syndrome.\(^2\) This acute myopathy syndrome is accompanied by a preservation in peripheral sensation, in contrast to critical care polyneuropathy, and may also be accompanied by an elevation in creatine kinase.\(^2,12\) This myopathic process is also termed acute quadriplegic myopathy syndrome (AQMS) and is distinct from prolonged paralysis due

![Figure 1. Patient enrollment.](Image URL)
to delayed drug clearance.³ AQMS may in part be related to an absence of myosin messenger RNA.¹⁴ Concomitant corticosteroid use appears to also play a role in this myopathic process, and is particularly important in the generation of prolonged paralysis in asthma patients treated both with NMB and corticosteroids.²,¹² A retrospective study¹⁵ found that 35% and 31% of patients with asthma concurrently receiving atracurium or vecuronium, respectively, (both nondepolarizing NMB agents) and corticosteroids had muscle weakness. Earlier speculation that this problem is confined to aminosteroid compounds such as vecuronium, due to their similarity in structure to corticosteroids,² has been largely dispelled by such findings. No cases of prolonged paralysis (due to drug clearance issues) or acute myopathy were identified in our group of paralyzed patients, despite 47% of the total enrollees receiving corticosteroids.

Other drugs in addition to steroids have been implicated in prolonging pharmacologic NMB, including aminoglycosides and clindamycin.⁸ The current study notes no differences in the use of either corticosteroids, aminoglycosides, or clindamycin in the two study groups.

The use of TOF monitoring in the study by Prielipp et al⁶ did not prevent the occurrence of prolonged muscle weakness in 2 of 28 and 13 of 30 ICU patients receiving cisatracurium and vecuronium, respectively. These episodes of muscle weakness were apparently independent of high-dose corticosteroid use.⁶ TOF monitoring, however, only occurred a minimum of every 8 hours in stable patients, with the authors suggesting that TOF monitoring does not prevent the occurrence of myopathy or polyneuropathy.⁶

More frequent monitoring, however, appears not

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<th>Table 1—Patient Demographics*</th>
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<td>Variables</td>
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<td>Mean age, yr</td>
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<td>Male/female sex</td>
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<tr>
<td>Underlying disease†</td>
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<tr>
<td>Pulmonary</td>
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<tr>
<td>Nonpulmonary</td>
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<tr>
<td>Indications for paralysis</td>
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<tr>
<td>Ventilator dysynchrony</td>
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<tr>
<td>Severity of illness</td>
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<td>APACHE II score at paralysis</td>
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<td>Mechanical ventilation days before paralysis</td>
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<td>Range</td>
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<td>Glomerular filtration rate, mL/min (upon entry)</td>
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<td>Medications</td>
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<td>Corticosteroid</td>
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<td>Aminoglycoside</td>
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<td>Clindamycin</td>
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<td>*Data are presented as mean ± SEM or No. unless otherwise indicated. NS = nonsignificant p value, p &gt; 0.05, comparisons made using unpaired t test with Bonferroni correction for multiple comparisons, χ², or Fisher exact test, as appropriate.</td>
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<td>†See “Results” section for specific pulmonary and nonpulmonary diagnoses.</td>
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<th>Table 2—Patient Outcomes After Paralysis*</th>
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<td>Variables</td>
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<tr>
<td>Recovery time, min</td>
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<tr>
<td>Mean total paralysis time, min</td>
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<tr>
<td>Mean total cisatracurium dose, mg</td>
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<td>Mean cisatracurium dose, µg/kg/min</td>
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<td>Milligram per kilogram cisatracurium dose</td>
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<td>Episodes of prolonged paralysis, No.</td>
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<td>*Data are presented as mean ± SEM unless otherwise indicated.</td>
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<td>†Comparisons were made using unpaired t test with Bonferroni correction for multiple comparisons, or Fisher exact test as appropriate, p &lt; 0.05 significant. See Table 1 for expansion of abbreviation.</td>
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to make TOF monitoring more useful, as noted in
the study by Strange and colleagues. 7 Minimum
required TOF monitoring every 4 h uncovered no
benefit to TOF monitoring. The TOF group and
the clinical assessment group, undergoing paralysis
with atracurium, demonstrated no differences in recovery
times, total dose of NMB agent used, or mean dosage
(micrograms per kilogram per minute) of atracurium
used. No cases of prolonged paralysis were reported.
Patients were not randomized but assigned by the
physician attending in the medical ICU.

Conflicting results are found in the randomized,
controlled ICU study by Rudis et al, 4 showing a
decrease in vecuronium use and recovery times in
the TOF-monitored group compared to clinical ti-
tration based on ventilator triggering. 4 However, this
study differs from the two prior studies 6, 7 in the less
frequent minimal required use of TOF (every 12 h)
and the paralytic agent utilized. The less frequent
use of TOF should lead to less effective monitoring
and increased recovery times (not less, as found),
compared to the preceding two studies. A likely
etiology of the discrepancy between these studies is
that vecuronium is dependent on adequate renal and
liver function for clearance, opposed to agents such
as atracurium and cisatracurium cleared indepen-
dently of end-organ function. 8 These later two agents
appear statistically less likely to be associated with
prolonged paralysis. 6

A strength of the current study is its confirmation
of the findings by Strange and colleagues 7 that TOF
provided no benefit over careful clinical assessment
(observation), even with monitoring every 4 h. Sim-
ilarly, our study finds TOF does not reduce recovery
times or doses of cisatracurium over patients moni-
tored by clinical assessment. The lack of randomiza-
tion in the study by Strange and colleagues 7 is
corrected in the present study.

An additional strength of the current study is the
accompanying power analysis. Strange et al 7 estimated
the need for 876 study patients to further test the possibility that TOF monitoring would be be-
 neficial in reducing the clinical recovery time noted in
their study (both group means ≤ 50 min). The post-study power analysis of the current study esti-
mates that our final smaller sample size is sufficient
to detect a change of ≥ 60 min between groups for
postparalysis recovery time. The mean duration of
paralysis of both groups was > 2.2 days, and mean recovery times were < 45 min. However, our small
sample size is potentially prone to type II (β) error.
This potential error is most pertinent in assessing a
difference between the TOF and clinical assessment
groups for postparalytic recovery times of < 60 min.
A recovery time of < 60 min in patients frequently
paralyzed for many days in the ICU setting is likely
not clinically or economically meaningful.

A problem encountered during the present study
was nursing compliance with TOF monitoring. Four
of the seven nonevaluable patients were excluded
due to nursing difficulties with TOF monitoring.
Monitoring errors occurred despite frequent nursing
in-services, and the use of both types of monitoring
in our ICU before this study started. Informal
discussions with the nursing staff cite technical and
interpretive problems with peripheral nerve stimu-
lation and the labor-intensive nature of TOF moni-
toring. A survey of critical care nurses notes that
almost half of surveyed nurses use TOF monitoring
every 30 to 60 min in patients receiving NMB. 16

Our study protocol purposely did not incorporate
a built-in wake up (NMB drug holiday) period for
our patients. It has been suggested that overdosing
of NMB could be avoided by allowing periods of
normal muscle function by limiting continuous NMB
to no more than 24- to 48-h periods or by frequent
use of a peripheral nerve stimulator. 2, 13 An older
consensus recommendation of a daily drug holiday
from NMB was made despite acknowledging the
absence of any convincing available data. 13 The more
recent guideline update 4 continues to suggest that a
drug holiday may decrease the incidence of AQMS,
but remains based on limited evidence. In order to
clarify answer the question of whether TOF moni-
toring or best clinical assessment was superior, inter-
nmitent discontinuance of NMB was not incorpo-
rated in our study. It should be noted, however, that
the potential beneficial effect of a drug holiday may be
greater for drugs, such as vecuronium and puncuro-
nium, which are dependent on end-organ clearance.

An additional problem is our primary reliance on
TOF monitoring to assess for prolonged paralysis from
pharmacologic overdose or, less likely, from acute
myopathy. We did not rely on pulmonary mechanics to
assess for prolonged paralysis or muscle weakness given
the confounders of sedation and narcotic use in all
patients. Further, time to extubation was not utilized
given the myriad problems in our critically ill popula-
tion, unrelated to paralytic use, potentially contributing
to the need for continued mechanical ventilation. Clin-
ical assessment was our primary diagnostic tool for
acute myopathy. Other more invasive indicators of
acute myopathy including elevated creatinine kinase
and electromyography and the more definitive indica-
tor, muscle biopsy, were not routinely utilized. No
patient required the consideration of a neurologic
consultation and of an electromyographic assessment
and/or muscle biopsy. Such a consideration would have
occurred only if four twitches were not seen within 3 h
of cisatracurium discontinuation. Our reliance on non-
invasive TOF monitoring enabled our successful efforts

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to have patient consent waived by our institutional review board. The resulting successful patient randomization is a significant asset to this study, but subtle acute myopathic problems may have been overlooked.

Additional limits to our study include not measuring total mean sedative dose or total mean narcotic dose in each group and the arbitrary termination of paralysis. Either midazolam or lorazepam could be used in any individual patient, making assessment of the final mean total sedation dose problematic. However, differences in mean total dose of sedation and type of sedation utilized would not have affected recovery of four TOF twitches after paralytic termination. Differences in total sedation dose or type of sedative used could have led to differences in total mean mechanical ventilation time after NMB termination, a parameter not assessed in this study. Similar considerations arise from our use of either morphine sulfate or fentanyl for pain relief.

Termination of NMB was arbitrary, and was at the discretion of the clinician caring for the patient. This may have introduced unanticipated bias. Our medical ICU philosophy has been to limit NMB duration to mitigate potential side effects. Therefore, the most likely bias introduced would be to limit NMB use (total dose or time) in all patients, not selectively in patients monitored by TOF or by clinical assessment. No noted significant difference in total paralysis time and total cisatracurium dose parameters, between the two groups, indicates absence of such bias (Table 2). Given the relatively small numbers in the two groups this could, however, reflect a type II error (ß error).

There are other limitations to our study. The MICU protocol and nursing education may have increased awareness of NMB complications compared to usual care. Our findings may not be applicable to paralytic agents other than cisatracurium (and likely atracurium). These two agents undergo Hofmann degradation and ester hydrolysis independent of end-organ function obviating problems with renal or hepatic insufficiency or failure. Alternately, agents such as vecuronium that require both liver and renal function for clearance may have more propensities for prolonged paralysis simply from inadvertent overdose. This may be particularly important in the intensive care setting such as ours where multisystem organ failure is common. Hence, patients undergoing paralysis with an agent requiring end-organ elimination, particularly if multisystem organ failure is present or imminent, may benefit from TOF monitoring.

We conclude, during paralysis with atracurium-based compounds in the intensive care setting, that frequent TOF monitoring offers no significant advantages over careful clinical assessment. Careful clinical assessment alone provides a reasonable approach to titrating cisatracurium (and atracurium) in the intensive care setting. These findings may not be applicable to other NMB agents, such as vecuronium and pancuronium, which are dependent on end-organ function for drug clearance.

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