Improved Neuromuscular Blockade Using a Novel Neuromuscular Blockade Advisory System: A Randomized, Controlled, Clinical Trial

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BACKGROUND: Conventional incremental bolus administration of neuromuscular blocking (NMB) drugs is associated with limitations in intraoperative control, potential delays in recovery, and residual blockade in the postanesthetic period. To overcome such limitations, we developed a novel adaptive control computer program, the Neuromuscular Blockade Advisory System (NMBAS). The NMBAS advises the anesthesiologist on the timing and dose of NMB drugs based on a sixth-order Laguerre model and the history of the patient's electromyographic responses. Here, we tested the hypothesis that the use of the NMBAS improves NMB compared to standard care.

METHODS: We conducted a prospective, randomized, controlled, blinded, parallel-group, clinical trial with $n = 73$ patients (ASA physical status I-III) undergoing abdominal surgery under general anesthesia ≥1.5 h with NMB using rocuronium. Patients were allocated to standard care or NMBAS-guided rocuronium administration. The primary outcome variable was the incidence of intraoperative events reflecting inadequate NMB. Secondary outcome variables included train-of-four (TOF) ratios at the end of surgery before reversal, the total doses of rocuronium, reversal agents, anesthetics and other drugs, the incidence of postoperative adverse events, and the incidence of anesthesiologist noncompliance with NMBAS recommendations.

RESULTS: Of 73 enrolled patients, $n = 30$ per group were eligible for analysis. Patient demographics were comparable between the groups. The incidence in total intraoperative events associated with inadequate NMB was significantly lower in the NMBAS group compared to standard care (8/30 vs 19/30; $P = 0.004$). Mean TOF ratios at the end of surgery before reversal were higher in the NMBAS group (0.59 [95% CI, 0.48–0.69] vs 0.14 [95% CI, 0.04–0.24]; $P < 0.0001$). Total administered doses of rocuronium, reversal drugs, and other drugs, and the incidence of postoperative adverse events were not different.

CONCLUSIONS: Compared to standard practice, NMBAS-guided care was associated with improved NMB quality and higher TOF ratios at the end of surgery, potentially reducing the risk of residual NMB and improving perioperative patient safety.

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Conventional incremental bolus administration of neuromuscular blocking (NMB) drugs, such as rocuronium, is associated with well-known shortcomings. These include limitations in intraoperative control and rapid adaptation to changing surgical conditions (including unanticipated termination of the procedure), fluctuations in plasma concentrations and the quality of blockade, possible inability to reverse intense blockade, potential delays in recovery, and a sizeable risk of residual blockade in the postanesthetic period.[1,2]

Automated drug delivery in the form of computer-guided administration and/or infusion represents an attractive strategy to overcome such limitations and

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improve the match between drug administration and the individual patient's response and requirement. Additional potential advantages of computer-guided drug administration include reduction in drug usage and costs, decrease in physician workload, relief from the distraction from physiological monitoring, facilitation of the safe use of drugs that can be difficult to administer manually due to low therapeutic indices, and minimization of the risk of drug errors. Drug errors are among the most frequent threats to patient safety in anesthesiology and often involve muscle relaxants.[3–5]

Computerized NMB drug administration has been attempted previously. Representative examples for such efforts include "bang-bang" on/off, proportional-integral-derivative and fuzzy logic controllers.[6–10] Whereas these controllers have achieved near constant levels of blockade in various experimental settings,[10–12] they are associated with significant constraints that thus far have impeded their utility in routine clinical practice. For example, most involve the use of single twitch stimulation to measure response (T1%). In addition to the often considerable associated setup time, the use of single twitch stimulation necessitates a stable control,[13] and T1% baseline stabilization requires up to 20 min between induction and NMB drug administration, unnecessarily exposing patients to the risks of an unprotected airway and creating unacceptable operating room time delays.[14] Furthermore, the typical controller set point is T1% = 10 (i.e., 90% single twitch suppression),[9,12,14–16] which represents a potentially nonreversible state. Finally, none of these technologies have been rigorously studied in a prospective, randomized, controlled fashion to demonstrate their superiority over routine clinical practice.

In an attempt to address these limitations, we have developed a novel adaptive control computer program, the Neuromuscular Blockade Advisory System (NMBAS).[17] As an intermediate step towards complete automation (i.e., closed-loop control) of NMB, the NMBAS advises the anesthesiologist on the timing and dose of NMB drugs such as rocuronium based on a sixth-order Laguerre model and the history of the patient's electromyographic (EMG) responses to conventional train-of-four (TOF) stimulation. The NMBAS system acts as a partial closed-loop controller, with the anesthesiologist closing the loop by completing (with or without modification) the administration recommended. Here, we conducted a prospective, randomized, controlled, blinded, parallel-group clinical trial to test the hypothesis that the use of the NMBAS improves NMB compared to standard care in the context of routine clinical practice.

METHODS

The study protocol was approved by the University of British Columbia and Providence Health Care Research Ethics Boards (both, Vancouver, B.C., Canada). Written informed consent was obtained from all subjects.

Modeling and Control Background

The modeling and control background of the NMBAS has been described previously.[17] In brief, models of each individual patient's response to rocuronium were used to predict drug dosing requirements. We used published pharmacokinetic-pharmacodynamic parameters[18] to derive the initial models. To identify the optimal model, we tested model structures (autoregressive exogenous, polynomial, and Laguerre models) of varying dimensions and parameters for their ability to best represent bolus response data with the least degree of complexity.[17] Patients' rocuronium responses were best represented by a sixth-order Laguerre model.[19–21]

Laguerre series can be seen as a generalization of a Fourier series. Whereas Fourier series use sine and cosine functions, the Laguerre series uses basis functions that have a finite temporal support (i.e., they eventually vanish) and resemble transient signals. Laguerre functions are thus very efficient at representing the transient response of dynamic systems while requiring a minimum of *a priori* information about the system to be represented. Hence, they are particularly amenable to adaptive control of time-varying, uncertain systems. Such representation forms the basis of adaptive control methodology that has proven very effective in the process industries over the last 20 yr. For the present application, the Laguerre-based model was used in a model-predictive control scheme that, based on the predicted evolution of the system, issues recommendations for rocuronium administration such that the requirement in terms of a desired NMB level are satisfied over a specified time horizon (see below). With a Laguerre model, the patient is modeled as a series of filters through which the inputs flow, where the number of filters used indicates the complexity of the system. Due to the orthogonal (i.e., nonconnected) nature of the filters, more filters can be added to produce better representation of the system at the expense of increased computation and diminishing value. In previous testing, we found that six filters, hence a sixth-order Laguerre model, produced exceptional fidelity to the patient data without great complexity.[17]

The NMBAS' adaptive control system consisted of a two-step adaptation. The initial patient model at the start of each case was constructed as an average of rocuronium dose-response measurements obtained from an existing bank of pilot data (step one). Intraoperatively, ulnar nerve TOF stimulation at 2 Hz was used to evoke adductor pollicis muscle contractions. The resulting EMG measurements (*cf.* below) were then used to further adapt the patient model in real-time through recursive least squares estimation with an exponential forgetting and resetting scheme

(step two).[22] An extended horizon controller (a predictive control algorithm using an assumed model of the process and assumed inputs to derive the future control signals)[23] used the updated model to project the response into the future and by back-calculation predict the dose of drug required to maintain NMB just below the selected constraint (TOF ratio, 0.1) for the next 20 min and until the anticipated end of surgery. A TOF ratio of 0.1 was chosen as a constraint for the adaptive controller to reflect a value at the most responsive end of the range of surgically useful and easily reversible levels of NMB, with minimal risk of patient motion.[24] The horizon of 20 min was selected as a minimum time interval between doses assumed to be easily acceptable to anesthesiologists without being perceived as inconvenient. The monitoring, modeling, and control procedures were repeated every 20 s.

Participants

Patients were screened for eligibility through interviews and examination of the hospital charts. Male and female patients were considered eligible for participation in the study if they were aged 18 yr or older, scheduled for abdominal surgery ≥1.5 h under general anesthesia with NMB, and ASA physical status I–III. Patients were excluded if they were pregnant, scheduled for intraoperative epidural anesthesia/analgesia, had a hypersensitivity or allergy to rocuronium or any component of its formulation or any other NMB drug, hepatic or renal failure, a Body Mass Index >35 kg/m^2, a history of neuromuscular disease, impaired neuromuscular response in the forearm, or decreased responsiveness to neuromuscular stimulation (e.g., due to peripheral neuropathy or myasthenia gravis), were taking drugs potentially interacting with rocuronium (including anticonvulsants, aminoglycosides, tetracycline, and vancomycin), or were unable to communicate or provide informed consent.

Interventions

Patients were randomly allocated by computer in blocks of four to either the control ("standard care") or NMBAS group. For patients allocated to the standard care group, anesthesiologists were instructed to provide NMB with the use of rocuronium according to their routine practice, based on clinical observation and measurements obtained from a standard handheld neuromuscular stimulator (Fisher & Paykel Healthcare, Auckland, New Zealand). In the NMBAS group, anesthesiologists administered bolus rocuronium doses guided by the NMBAS recommendations, subject to their clinical judgment (*cf.* below). All patients received a standard balanced general endotracheal anesthetic (Aestiva®/5 anesthesia delivery system; GE Healthcare, Madison, WI). Patients were induced with fentanyl 1–2 μg/kg, propofol or thiopental titrated to effect, rocuronium (see below), and maintained with desflurane or sevoflurane to keep vital signs within 20% of preoperative baseline values. Adjuvant drugs were administered as per routine clinical practice and their use compared between the groups.

In both groups, standard stimulation protocols (TOF and posttetanic count) were monitored by a research associate throughout the case *via* the NMBAS computer program but not displayed to the anesthesiologist or surgeon. Ulnar nerve stimulation was enacted and sensed with the use of EMG at intervals of 20 s with the use of a Datex-Ohmeda S/5™ neuromuscular transmission module (M-NMT; GE Healthcare, Madison, WI). A portable personal computer (ThinkPad™, IBM, Armonk, NY) was interfaced to the S/5 for recording and analysis of the measured EMG responses and other physiological data. Inhaled drug concentrations obtained from the S/5 multigas measurement Compact Airway Module were recorded throughout each case and compared between the groups. Figure 1 provides a schematic illustration of the general principle of the NMBAS' setup and function.

The initial rocuronium dose was based on the standard recommended dose for tracheal intubation ($2 \times ED_{95}$ = 0.6 mg/kg). Recommendations for subsequent doses (minimum time interval, 20 min; *cf.* Modeling and Control Background) were based on the patient's responses to the NMB drug, with the aim of maintaining the TOF ratio <0.2 with at least two measurable twitches to achieve a balance between surgical requirements and reversibility (controller constraint, TOF ratio = 0.1; *cf.* above). The anesthesiologists had the choice of adopting, modifying, or disregarding any advice of the NMBAS.

Objectives and Outcomes

The overall objective was to test the hypothesis that NMBAS-guided care improves NMB compared to standard care in the context of routine clinical practice. The primary outcome variable was the incidence of intraoperative events reflecting inadequate NMB, defined as the occurrence per patient of one or more of the following: inadequate surgical relaxation, patient motion (as judged by the surgeon), breathing against the ventilator (detected by capnography as plateau notches or unwanted spontaneous dyssynchronous respiratory efforts), and bucking or coughing on the ventilator (as assessed with the aid of airway pressure monitoring and capnography by the attending anesthesiologist, see below).

Secondary outcome variables included TOF ratios at the end of surgery (last stitch) before any reversal; total administered doses of rocuronium, reversal drugs, and other drugs; the incidence of postoperative adverse events; and the incidence of and reasons for anesthesiologist noncompliance with the NMBAS recommendations. We also compared the groups in the timing of the following perioperative events relative to operating room entry: induction of anesthesia; tracheal intubation, start and completion of surgery

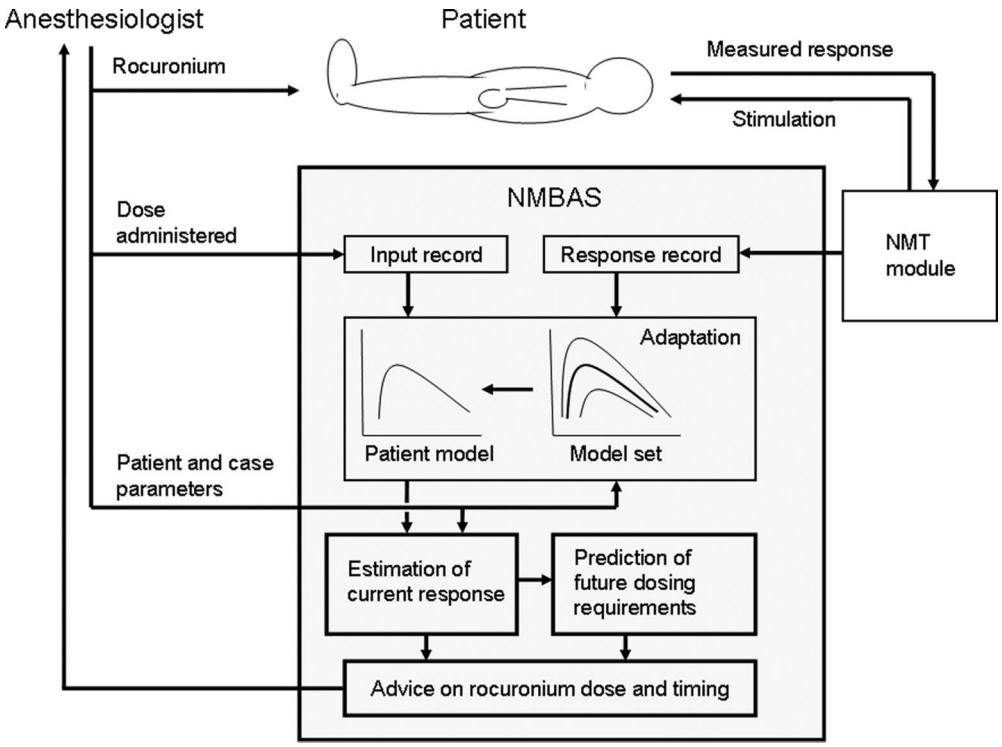

Figure 1. Schematic illustration of the setup and operation of the NMBAS. NMBAS = Neuromuscular Blockade Advisory System; NMT = neuromuscular transmission. For details, see body text.

(incision/last stitch); extubation; and postanesthesia care unit admission.

Patients, surgeons, and postanesthesia care unit/surgical daycare nurses were blinded to group allocation. The nonblinded attending anesthesiologists, responsible for the individual patients' anesthesia care, had no knowledge of the EMG data from the M-NMT module interfaced with the NMBAS computer (*cf.* Interventions), had no vested interest in the NMBAS or the outcome of the trial, and did not participate in data entry, postoperative assessment, or statistical analysis. The NMBAS system with its associated computer hardware was set up in both groups to further minimize potential bias.

Statistical Analyses

The final target sample size for this trial was based on pilot data and data from an interim analysis performed on 10 eligible patients per group and projected to detect a minimum important difference of 25% in the incidence of intraoperative events associated with inadequate NMB (*cf.* above) between the two groups. In order to achieve 80% power and a type I error not exceeding 5%, a minimum of $n = 30$ valid patients per group were required. In order to maximize power and compensate for patients to be excluded from the analysis, $n = 73$ patients were enrolled.

Statistical analysis of the primary outcome variable was performed on an intention-to-treat basis. Categorical data were analyzed with the use of the Chi-square test. We used the Kolmogorov-Smirnov test and assessed kurtosis and symmetry of continuous data to test if values came from a Gaussian distribution. Normally distributed continuous data were compared with Student's *t*-test. Nonnormally distributed data were analyzed with the Mann-Whitney rank test. Statistical tests were two-tailed and comparisons considered statistically significant at $P < 0.05$. Unless mentioned otherwise, data are expressed as mean ± SD. The data were analyzed using Prism software (GraphPad, San Diego, CA).

RESULTS

Patient Demographic and Surgical Data

Seventy-three patients provided informed consent to participate in the trial. Thirteen were excluded due to protocol violations, lead failures/dislodgements, and possible breaches of blinding (NMBAS EMG data were inadvertently displayed on the anesthesia monitor, and hence visible to anesthesiologists in five cases). There were 24 women and 6 men in the standard care group, and 26 women and 4 men in the NMBAS group. Sixty-five percent of the surgeries were gynecological; the remainder comprised bowel resections/repairs and cholecystectomies. Both groups were statistically similar in terms of patient demographic data (Table 1), the distribution of surgical procedures between the groups (data not shown), and the timing of perioperative events (Table 2).

Primary Outcome

The incidence of total intraoperative events reflecting inadequate NMB was significantly lower in the

Table 1. Patient Demographic Data

	Standard care	NMBAS
Sex (F/M)	24/6	26/4
Age (yr)	51 ± 13	53 ± 13
Weight (kg)	68 ± 13	66 ± 12
Height (cm)	163 ± 10	164 ± 8
ASA physical status (class I/II/III)	10/16/4	8/19/3

Data are presented as mean ± SD where appropriate.

Each group, $n = 30$. All variables, $P > 0.05$.

NMBAS = Neuromuscular Blockade Advisory System.

Table 2. Timing of Perioperative Events

	Standard care	NMBAS
Induction	12 ± 7	11 ± 5
Intubation	16 ± 7	17 ± 7
Start of surgery (incision)	35 ± 9	35 ± 8
Completion of surgery (last stitch)	145 ± 43	142 ± 37
Extubation	154 ± 45	154 ± 38
Interval between intubation and extubation	138 ± 46	138 ± 37
PACU admission	161 ± 42	164 ± 35

Data are presented in minutes as mean ± SD relative to the time of patient entry into the operating room.

NMBAS = Neuromuscular Blockade Advisory System; PACU = postanesthesia care unit.

Each group, $n = 30$. All variables, $P > 0.05$.

Table 3. Incidence of Intraoperative Events Reflecting Inadequate Neuromuscular Blockade

	Standard care	NMBAS
Patient motion	5	4
Inadequate surgical relaxation	10	3*
Breathing against ventilator	15	6*
Bucking on the ventilator	3	2
Total number of events	19	8†

Incidences were defined as the occurrence of one or more event per category and patient. For the total number of events, note that each patient could have experienced more than one event.

Each group, $n = 30$.

NMBAS = Neuromuscular Blockade Advisory System.

* $P < 0.05$; † $P < 0.01$; all other variables, $P > 0.05$.

NMBAS group compared to standard care (8/30 or 27% vs 19/30 or 63%; Chi-square test, χ^2 [1, $n = 60$] = 8.15, $P = 0.004$). This was primarily due to a reduction in the incidence of patients breathing against the ventilator (6/30 vs 15/30; χ^2 [1, $n = 60$] = 6.47, $P = 0.01$). In 10 of 30 standard care patients, surgeons complained about inadequate relaxation, compared to 3 of 30 patients in the NMBAS group (χ^2 [1, $n = 60$] = 4.82, $P = 0.028$). There were no significant differences in the incidences of patient motion or bucking on the ventilator. The details of these data appear in Table 3. Examples of a case from either group are illustrated in Figure 2.

Secondary Outcomes

Mean TOF ratios at the end of surgery (last stitch) before any reversal were higher in the NMBAS group (0.59 [95% CI, 0.48–0.69; $n = 29$] vs 0.14 [95% CI, 0.04–0.24; $n = 25$]; Mann-Whitney test, $P < 0.0001$). Likewise, the proportion of patients with a TOF ratio ≥0.7 was significantly higher in the NMBAS group (9/29 or 31% vs 1/25 or 4%; $P = 0.01$). Total administered doses of rocuronium and reversal drugs were not different; however, whereas all patients in the NMBAS group received a reversal drug, 8/30 patients (27%) in the standard care group did not (Chi-square test, χ^2 [1, $n = 60$] = 9.23, $P = 0.002$; Table 4). Both groups were similar in inhaled anesthetic use (average of median MAC per patient: standard care, 1.01 [95% CI, 0.90–1.13] vs NMBAS, 0.97 [95% CI, 0.87–1.06]; $n = 30$ per group; t (58) = 0.60, $P = 0.55$) and total administered doses of other drugs (detailed list not shown), including IV anesthetics and opioids (all drugs, $P > 0.05$). There were no differences in the incidence of postoperative adverse events. The most common adverse event was postoperative nausea, which occurred in 4/30 (13%) standard care patients vs 6/30 (20%) NMBAS patients (χ^2 [1, $n = 60$] = 0.48, $P = 0.49$). One patient in the standard care group and two patients in the NMBAS group received IV fluid for postoperative hypotension. No respiratory or other adverse events were noted. There were no differences in postoperative analgesic consumption in the postanesthesia care unit (data not shown).

The NMBAS provided 83 postintubation rocuronium dosing recommendations for maintenance of NMB in the $n = 30$ NMBAS group cases. One of the 83 NMBAS recommendations (1.2%) was not adopted because the anesthesiologist felt that the patient was adequately paralyzed. Two of 83 (2.4%) NMBAS recommendations were not followed because the recommended doses were perceived as being of little clinical significance. On eight occasions, anesthesiologists elected to discard the last rocuronium dosing advice in a case due to proximity to the actual (vs predicted) end of surgery.

DISCUSSION

In this prospective, blinded, randomized, controlled clinical trial, a novel adaptive computer-controlled advisory system, the NMBAS, improved NMB control compared to standard care in the context of routine clinical practice. NMBAS-guided care significantly reduced the incidence of intraoperative events reflecting inadequate NMB, particularly breathing against the ventilator and surgeons' complaints about inadequate relaxation. Patients who received NMBAS-guided rocuronium administration also had significantly higher TOF ratios before reversal and were more likely to have a TOF ratio more than 0.7 before reversal, consistent with a decrease in the likelihood of difficulty with reversal and residual paralysis in the postanesthetic period.[1,2,25] Hence, in addition to improving the quality and control of NMB, NMBAS-guided rocuronium administration was associated with the potential to improve perioperative

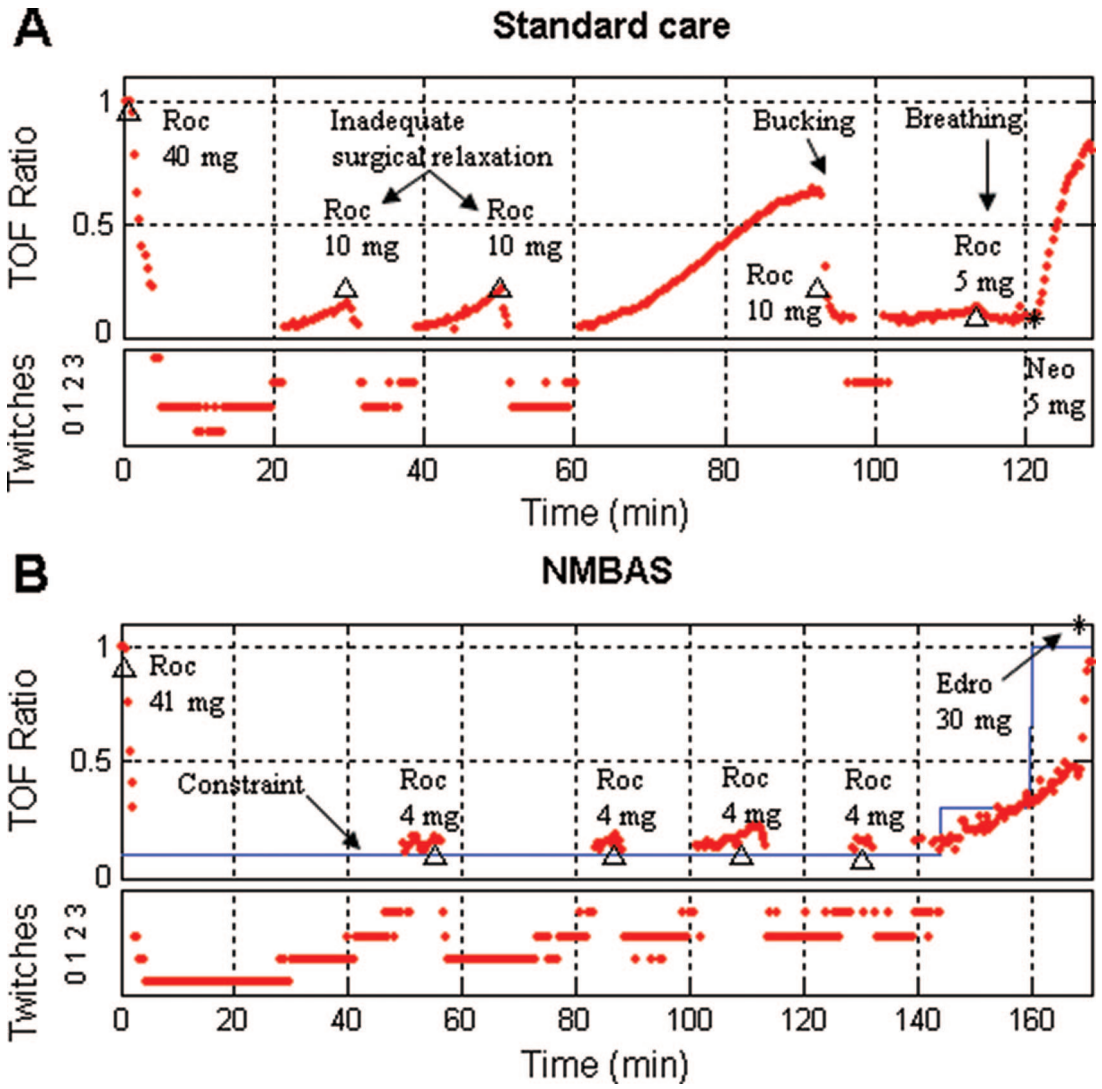

Figure 2. Case illustrations. TOF = train-of-four; Roc (open triangle) = rocuronium, Neo (asterisk in panel A) = neostigmine, Edro (asterisk in panel B) = edrophonium, and NMBAS = neuromuscular blockade advisory system. The ordinate scale represents the TOF ratio (range, 0–1; solid dots); twitch counts <4 are depicted underneath in a categorical manner (3, 2, 1, or 0). At the beginning of either case, standard rocuronium intubation doses (0.6 mg/kg) were administered, followed by smaller maintenance doses. (A) The standard care case represents a 47-yr-old female undergoing a total abdominal hysterectomy and bilateral salpingo-oophrectomy. Arrows indicate occurrences of events associated with inadequate neuromuscular blockade (*cf.* body text). At approximately 30 and 50 min, the surgeon complained about inadequate relaxation (TOF ratios, approximately 0.2), which was followed by the attending anesthesiologist administering repeat rocuronium doses. During the second half of the case, the patient reached TOF ratios as high as 0.7, bucking against the ventilator at approximately 90 min, and breathing against the ventilator at approximately 112 min. Both events were followed by repeat rocuronium administration. (B) The NMBAS case illustrated represents a 43-yr-old woman undergoing a total abdominal hysterectomy. The solid line (arrow) denotes the NMBAS constraint (TOF ratio, 0.1). There were no intraoperative clinical events associated with inadequate neuromuscular blockade, and the patient spent the majority of the case with a response between two twitches and the selected constraint (TOF ratio, 0.1), indicative of a reversible state. Note how the individual incremental repeat rocuronium doses recommended by the NMBAS were significantly smaller than a typical maintenance dose of 0.2 mg/kg and closely follow the preset 20 min horizon (the selected minimum interval between two subsequent doses), indicating continuous adaptation of the controller to the patient's responses. The anesthesiologist adopted all NMBAS recommendations.

patient safety by decreasing the chance of postoperative weakness.

The closest commercial implementation of automated drug administration at present is target-controlled infusion (TCI), which is driven by a mathematical model to provide a desired drug concentration at a targeted tissue.[26] TCI has not yet been approved for use in North America.[27] The NMBAS differs significantly from TCI systems. First, the NMBAS is a feedback system as it computes drug dosing to achieve and maintain the degree of NMB below a selected constraint. In contrast, TCI uses an open-loop system that computes drug dosing to achieve a simulated plasma or effect-site concentration. Second, in the NMBAS, drug dosing is based on the actual patient response, whereas TCI is based on noncalibrated standard pharmacokinetic-pharmacodynamic models that have been shown to be inaccurate.[28] Third, the NMBAS keeps the anesthesiologist

Table 4. Total Administered Rocuronium and Reversal Drug Doses

	Standard care	n/30	NMBAS	n/30
Rocuronium (mg)	60 ± 26	30	54 ± 17	30
Rocuronium normalized (mg/kg)	0.87 ± 0.29	30	0.81 ± 0.24	30
Neostigmine (mg)	3.4 ± 1.2	12	3.2 ± 1.0	20
Edrophonium (mg)	46 ± 18	10	37 ± 7	10
Reversal drug equivalent (mg)[a]	0.86 ± 0.73	22	0.91 ± 0.37	30[b]

Data are presented as mean ± SD where appropriate.

NMBAS = Neuromuscular Blockade Advisory System.

[a] Since both neostigmine and edrophonium were used as per routine clinical practice, their doses were normalized to equivalent doses based on their relative equipotency ratio of 16.[33]

[b] Eight patients in the standard care group versus none in the NMBAS group received no reversal drug; Chi-square test, $P = 0.002$ (*cf.* body text); all other categorical variables and all doses, $P > 0.05$.

"in the loop," which introduces human wisdom to the process and provides a safety check for a system in which frequent unanticipated changes can occur. Finally and importantly, because the NMBAS is adaptive, it "learns" from the individual patient, i.e., after automatically selecting the best model from its database, it builds a new model for each patient. Use of the NMBAS will thus result in the automatic development of a large body of patient data that can then be analyzed to refine the choice of initial model for a given patient. The choice of the Laguerre model is key to the success of this adaptation as it provides a very flexible representation, easily describes time delays, and ascertains stability of the identified model. Laguerre-based adaptive control as implemented in the NMBAS not only results in improved control for an individual over time, but also in an improvement for subpopulations of patients as the control database for a particular application increases. For example, a *post hoc* review of our rocuronium database raised the possibility that patients with a high Body Mass Index may benefit from specific model modification (data not shown). Incorporating such subpopulation modification in the initial model will in turn improve control for individuals and add to our knowledge of drug-pathology interactions. Similar refinements are possible for the effects of age, gender, ethnicity, renal function, etc.

All patients in the NMBAS group received reversal drugs compared to 73% of the patients in the standard care group. This is surprising because patients in the NMBAS group had significantly higher TOF ratios before reversal compared to standard care patients. It is conceivable that anesthesiologists caring for NMBAS patients practiced more conservatively (due to the apparent deviation from standard care associated with a novel technology) and were hence biased towards reversal drug administration; however, this remains speculative. On the other hand, anesthesiologists' compliance on the whole with the NMBAS and its recommendations was high, which provides an indication of the system's overall clinical applicability and utility.

Two potentially confounding factors for the EMG measurements in the present study were electrocautery effects and patient repositioning. Electrocautery produces electrical noise that may interfere with EMG signals. This can decrease the accuracy of measurements and increase the difficulty in controlling the level of NMB. Likewise, patient repositioning can cause a shift in the relative position of the stimulation electrodes to the stimulated nerve or sensed muscle, potentially impacting measurements. Whereas it would have been possible to use acceleromyography for the NMBAS instead of EMG, the latter is more reliable, more accurate, and significantly less prone to interference by external disturbances such as movement; therefore, it is the preferred method for feedback control systems.[29] In the present trial, both the NMBAS and control groups were equally exposed to these factors. The NMBAS may receive an error message in such events; it then produces a "no" signal and skips its adaptation step as no new, useful data are available. Instead, the NMBAS updates its model of the patient's state according to the data available before this measurement. However, because the NMBAS group was more reliant upon the sensor for its decision making and prediction than the standard care group, it was more vulnerable to the influence of electrocautery and patient repositioning. Thus, our finding that the NMBAS provided better care despite these limitations is further indication of the system's clinical utility, robustness, and ease of use. Likewise, the use of readily available monitors was deliberately chosen to simplify the clinical implementation of the system and test its efficacy in the context of routine anesthesia practice. We are aware of the complexity and controversies regarding the optimal assessment of NMB.[30] However, in addition to the demonstrated clinical effectiveness, the use of the NMBAS produced no delays or prolongation of anesthesia time compared to standard practice (*cf.* Table 2), an important consideration in today's operating room economics climate.

The limitation of drug administration in the current trial to a bolus injection at no less than 20 min intervals significantly restrained the NMBAS' potential in terms of control performance and its capability to adapt. Despite these restrictions due to such a relatively long control horizon, the system produced positive clinical outcomes. Switching to computer-controlled continuous infusion with markedly increased control action frequency will greatly improve both adaptation and control performance of the system in the future. Such a system could become a completely closed-loop control system. However, we believe that for safety reasons, the attending anesthesiologist will always

have to be able to override the system. Furthermore, computer-controlled infusion can never anticipate all clinical conditions within its prediction horizon (e.g., premature surgical closure; anaphylaxis; etc.) and thus the anesthesiologist will always be required as the ultimate clinical decision maker.

The development of a closed-loop infusion system for NMB drugs has been a focus of other investigators. For example, Eleveld et al. reported on the stable function of a closed-loop NMB drug controller based on randomly generated pharmacokinetic-pharmacodynamic rocuronium models.[31] However, the controller was fixed (i.e., nonadaptive) and the clinical results came from a nonrandomized, noncontrolled study with a limited sample size (n = 15). Subsequently, Schumacher et al. presented the design of a system based on single twitch suppression (T1%) control using linear quadratic state feedback with integral action with clinical results on 15 patients.[14] Good tracking of a T1% set point of 10% was achieved. No control group was used and no analysis of clinical outcomes performed. Finally, in the most recent published work on the topic at the time of writing, a fuzzy controller trained on 100 simulated patients was tested on 500 simulated patients.[32] Training was performed using a resource-intensive and difficult-to-tune evolutionary algorithm. No clinical results were reported. Hence, in addition to some of the inherent technological limitations of these systems compared to the NMBAS' Laguerre-based adaptive control platform, the clinical superiority of these systems compared to routine practice has not been established.

The principles and control algorithms developed for the NMBAS are applicable to many drug applications other than NMB drugs which share similar onset times, durations of action, and frequency responses of the drug effect sensor. Examples that are within the capabilities of this technology include control of depth of anesthesia/hypnosis, control of arterial blood pressure, treatment of dysrhythmias, administration of antianginal/-ischemic drugs, and anticonvulsive medications. Therefore, the NMBAS' Laguerre-based adaptive control technology represents a general platform from which to develop other automatic drug delivery systems for the operating room, intensive care unit, or, eventually, ambulatory use. In general, we believe that this technology has the potential to greatly enhance patient safety, e.g., by reducing the risks of unwanted adverse drug effects and drug errors, by facilitating the safe use of drugs that are difficult to administer, by permitting health care staff to work more efficiently and with a reduced workload, and by compensation for human shortcomings with computer strengths, such as quick and accurate complex redundant calculation as well as unlimited attention span and vigilance. In this sense, the present study allows for future investigations into the impact of Laguerre-based adaptive control technology on patient safety in the perioperative setting.

In conclusion, in a randomized, controlled, clinical trial, administration of the NMB, rocuronium, guided by a novel adaptive control system, the NMBAS, was associated with improved NMB quality and higher TOF ratios at the end of surgery compared to standard practice in patients undergoing abdominal surgery under general anesthesia. This study illustrates the principal feasibility of such a system and marks the transition for adaptive process control of anesthetic medications from a theoretical possibility to a demonstrated practicality.

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