A Close Relationship Between Post-tetanic Twitch and Train-of-Four Responses during Neuromuscular Blockade by Vecuronium

Hidenori TOYOOKA, Yoshihiro NOGUCHI,
Toshiya EBATA and Keisuke AMAHA

The relationship between post-tetanic twitch (PTT) and train-of-four (TOF) responses after intravenous administration of vecuronium were studied using EMG in 20 patients under nitrous oxide and enflurane anesthesia. After the initial dose (0.2 mg·kg^{-1}) of vecuronium, the detectable first twitch of PTT (PTT_1) always preceded that of TOF (TOF_1) with the mean time interval of 10.7 ± 2.6 min. The post-tetanic count (PTC) which coincided with the first appearance of TOF_1 was 9.4 ± 2.6. After the appearance of TOF_1, the magnitude of TOF_1 was almost identical to that of PTC_{10} until full recovery from neuromuscular blockade was observed, whether the supplemental doses of vecuronium (0.03–0.04 mg·kg^{-1} i.v.) were administered or not. The magnitude of TOF_2 was slightly lower than that of PTC_{20}. These results suggest that there is a close relationship between these two types of response, and by evaluating not only PTC but also the magnitude of each PTT, the recovery of TOF responses can be predicted and its extent be estimated fairly accurately. (Key words: post-tetanic twitch, post-tetanic count, train-of-four, vecuronium)

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When neuromuscular blockade is relatively intense and no response to single twitch or train-of-four (TOF) stimulation can be obtained in the arm, these conventional stimulation methods have limited value in evaluation of the degree of neuromuscular blockade. The recent advent of shorter-acting neuromuscular blocking agents may necessitate more integrated intra-operative clinical monitoring of the wide range of neuromuscular blockade by using different modalities of stimulation in sequence or even simultaneously. Post-tetanic twitch (PTT) response and the number of detectable responses of PTT (i.e. post-tetanic count, PTC) have been known to be a valuable methods for the evaluation of intense neuromuscular blockade[1,2]. It has also been shown that there is a close correlation between PTC and TOF during recovery from neuromuscular blockade caused by pancuronium and atracurium in adults[1,3], and by atracurium, vecuronium and pancuronium in children[4–6].

The objective of this study was to determine whether there is a consistent rela-

Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Address reprint requests to Dr. Toyooka: Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113 Japan

tionship between the first appearance time of TOF_1 and the number of detectable responses to PTT, and whether there is any relationship between the magnitudes of these responses during the recovery period from neuromuscular blockade with vecuronium in adult patients.

Materials and Methods

With institutional review board approval and written informed consent, 20 adult patients (9 male and 11 female), ASA class I or II, scheduled for elective lower abdominal or ophthalmological procedures entered the study. None of the patients had neuromuscular, renal or hepatic disorders or received any medication that might alter neuromuscular transmission.

All the patients were premedicated with hydroxyzine (1 $mg \cdot kg^{-1}$) and atropine sulfate (0.5 mg) i.m. 1 hr pre-operatively. On arrival to the operating room the stimulating surface-electrodes were sited on ulnar nerve at the elbow and recording electrodes on the corresponding abductor digiti minimi muscle. After induction of anesthesia with sodium thiopental (5 $mg \cdot kg^{-1}$) the ulnar nerve was stimulated supramaximally with an electrical stimulator (SEN-3201, Nihon-Kohden Inc. Tokyo). Rectangular pulses of 0.1 msec duration were automatically triggered by a computer in such a way to produce two patterns of electrical stimulation, i.e., TOF and PTT, as will be described below. When the response to TOF stimulation was stable, the magnitude of the first twitch of the train was taken as the control twitch height (T_0). Vecuronium, 0.2 $mg \cdot kg^{-1}$ i.v., was then administered to facilitate endotracheal intubation. Anesthesia was maintained by inhaling nitrous oxide 66% in oxygen and enflurane 0.5–1.5%, supplemental fentanyl (2–4 $\mu g \cdot kg^{-1}$) was administered as appropriate. Patients were placed on controlled ventilation to maintain normocarbia as measured by end-tidal CO_2 and intermittent arterial blood gas analyses. Rectal temperature was maintained between 35.5 and 36.8°C with warming blankets. In patients who needed further muscle relaxation additional vecuronium (0.03 to 0.04 $mg \cdot kg^{-1}$) was administered up to four times when the first response to TOF stimulation (TOF_1) returned to around 25% of T_0. During the first 5 min after obtaining T_0, TOF stimuli were applied every 5 sec to monitor the proper relaxation for endotracheal intubation. After 5 min from obtaining T_0, the interval of TOF stimuli were changed to 30 sec and PTT stimuli were substituted for TOF stimuli every 150 sec. This pattern of stimulation was continued until the end of the anesthesia, thereafter all the patients were ventilated with 100% oxygen, and were given 1 mg of atropine sulfate and 2 mg of neostigmine i.v. for the reversal of possible residual curarization.

For TOF stimulation, a series of 4 pulses was applied at 2 Hz for 2 sec[7]. For PTT, a tetanic stimulus (50 Hz) was applied for 5 sec, and after the interval of 3 sec, single twitch stimuli (1 Hz) were applied for 20 sec[1]. The EMG response of each stimulus was amplified via isolated differential amplifier (AVB-11, Nihon-Kohden Inc., Tokyo) and displayed on a storage oscilloscope (VC-11, Nihon-Kohden Inc., Tokyo). These EMG signals were then gated (gate open from 3 to 25 msec after test stimuli) to reduce the stimulation artifact, rectified and integrated for each single response, using specially designed integrator with reset and sample hold circuit controlled by digital commands from a computer. Integrated data sets of either TOF or PTT responses were displayed on a monitoring oscilloscope and were stored in a hard disk. A personal desk-top computer (PC-9801 UX, NEC Inc., Tokyo) was used for overall control of automatic stimulation-data collection sequences, and also for later data analysis. Verifications of these data sets were conducted by automatic analysis of the trains of responses to reject the EMG data which contained noise from electrocauteries. Trains of either TOF or PTT responses which could not be curve-fitted with single exponential decay equation were automatically rejected, as these were considered to have been contaminated with noises. Trains of PTT were paired with those of TOF

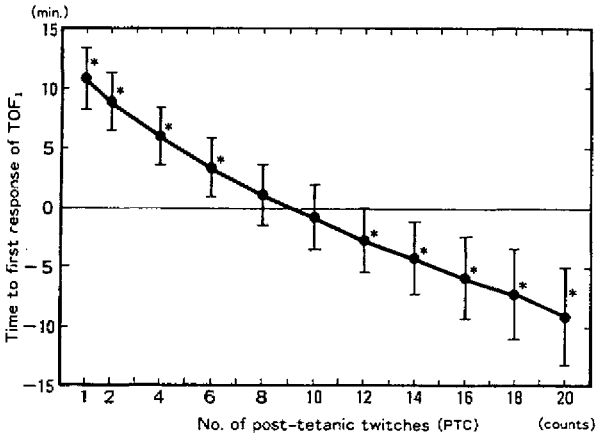

Fig. 1. Relationship between detectable number of post-tetanic twitch responses (=PTC) and the time interval to the first response of TOF_1 in 20 patients after the initial dose of vecuronium, 0.2 $mg \cdot kg^{-1}$, i.v. (Mean ± SD, n=20).

*: significantly different from 0 ($P < 0.01$).

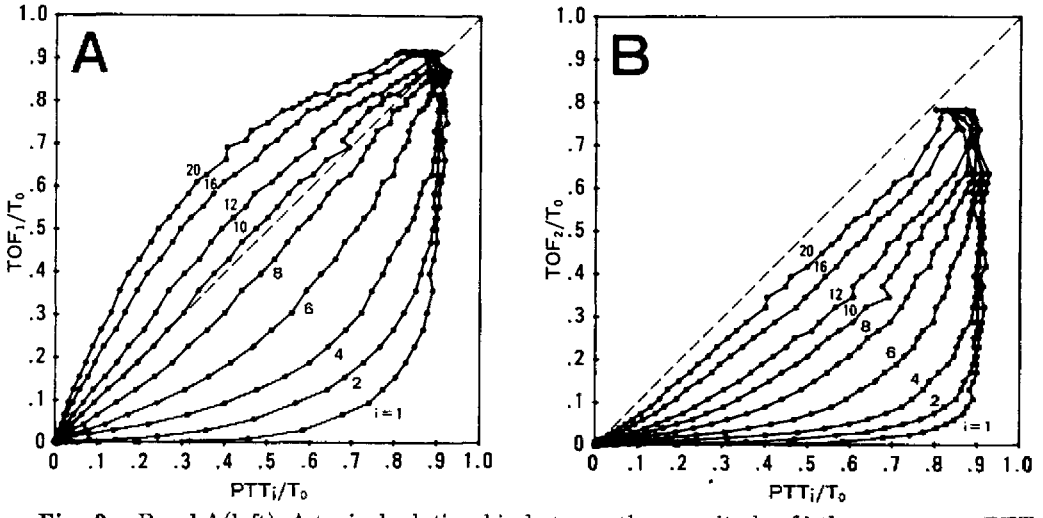

Fig. 2. Panel A(left): A typical relationship between the magnitude of i-th responses to PTT (=PTT_i) and that of TOF_1 after 0.2 $mg \cdot kg^{-1}$ of vecuronium, obtained at intervals of 2.5 min during the whole recovery period from total neuromuscular blockade until almost full recovery of TOF_1 was observed. Magnitudes of responses were standardized by dividing with that of the control twitch (=T_0).

Panel B(right): A typical relationship between the standardized magnitude of PTT_i and that of TOF_2 in the same patient.

obtained 30 sec previously and these were regarded as data sets obtained simultaneously. Relationship between the standardized magnitudes of i-th response of PTT (PTT_i/T_0, i=1 – 20) and those of j-th response of TOF (TOF_j/T_0, j=1 – 4) at any given time was sought on two-dimensional plots of these variables. The response to electrical stimulus was considered to be detectable when its magnitude was larger than or equal to 1.0% of that of T_0.

Statistical analysis was performed by using standard single variative regression analysis, analysis of variance and paired t-test, $P < 0.05$ being considered significant. All results were expressed as the mean ± SD.

Results

The mean age of the patients was 46.4 ± 19.9 yr, and the mean body weight was 54.8

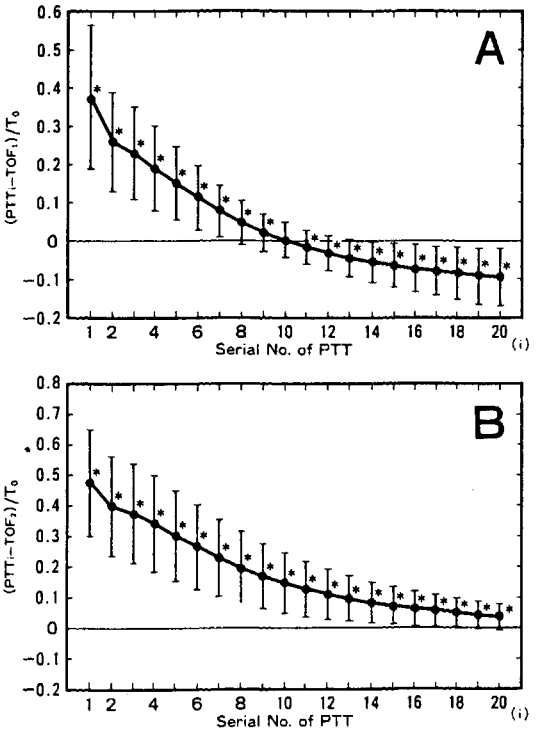

Fig. 3. Panel A(top): Mean difference between the standardized magnitude of PTT_i and that of TOF_1 plotted against serial number of PTT. Data were collected every 2.5 min in 20 patients during the period when any detectable response to TOF_1 was observed, either after the initial or after the supplemental administration of vecuronium. (579 pairs for each serial number of PTT, Mean ± SD).

Panel B(bottom): Mean difference between the standardized magnitude of PTT_i and that of TOF_2 plotted against serial number of PTT. Data were collected every 2.5 min in 20 patients during the period when any detectable response to TOF_2 was observed (438 pairs for each serial number of PTT)

*: significantly different from 0 ($P < 0.01$).

± 13.0 kg. The EMG-monitored anesthesia time for each patient was 199.4 ± 65.1 min on an average (range: 115–345 min). Only initial dose of vecuronium was administered in 7 patients, and additional doses were administered up to 4 times in 13 patients. The mean total dose of vecuronium was 13.4 ± 3.7 mg. In each patient, 8.4 ± 3.5% of data sets were rejected automatically as having been contaminated with noises of electrocautery. These rejected data sets were mainly obtained during the period of skin incision and other initial surgical procedures when there was no response to either PTT or TOF, and posed no serious problems for the following data analysis. In all of the patients the magnitude of TOF_1 returned to at least 80% of T_0 after neostigmine, 2.0 mg i.v.

After 124 ± 22 sec following initial administration of vecuronium, 0.20 $mg \cdot kg^{-1}$ i.v., all of the four responses of TOF disappeared almost simultaneously, with little fade if any. The detectable first response to PTT stimulation (PTT_1) always preceded the detectable TOF_1 in 20 patients, and appeared 27.8 ± 9.3 min after the initial administration of vecuronium. The TOF_1 appeared 10.7 ± 2.6 min after the appearance of PTT_1. The magnitude of PTT_1 was 32.4 ± 8.0% of T_0 at the time when the first TOF_1 reappeared.

The PTC which coincided with the first appearance of TOF_1 was 9.4 ± 2.6 (range 4–14). Figure 1 summarizes the mean time to the appearance of the first detectable TOF_1 as a function of the number of PTT responses present (i.e. PTC) in 20 patients after the initial dose of vecuronium was given.

A typical relationship between the standardized magnitude of TOF_1 and that of i-th responses to PTT (PTT_i), in a patient who was given only initial dose of vecuronium is shown in figure 2A. The data were obtained at intervals of 2.5 min during the whole period from total neuromuscular blockade until almost full recovery of the TOF_1 was observed. It is noteworthy that the magnitudes of PTT_{10} showed almost linear relationship with, and were almost identical to, those of TOF_1 during the whole recovery period from neuromuscular blockade by vecuronium.

The relationship between the standardized magnitude of TOF_2 and that of PTT_i in the same patient is shown in figure 2B. The magnitude of PTT_{20}, which was the last response of PTT we observed in this study, was most similar to the magnitude of TOF_2, although the former showed a slightly higher value than the latter.

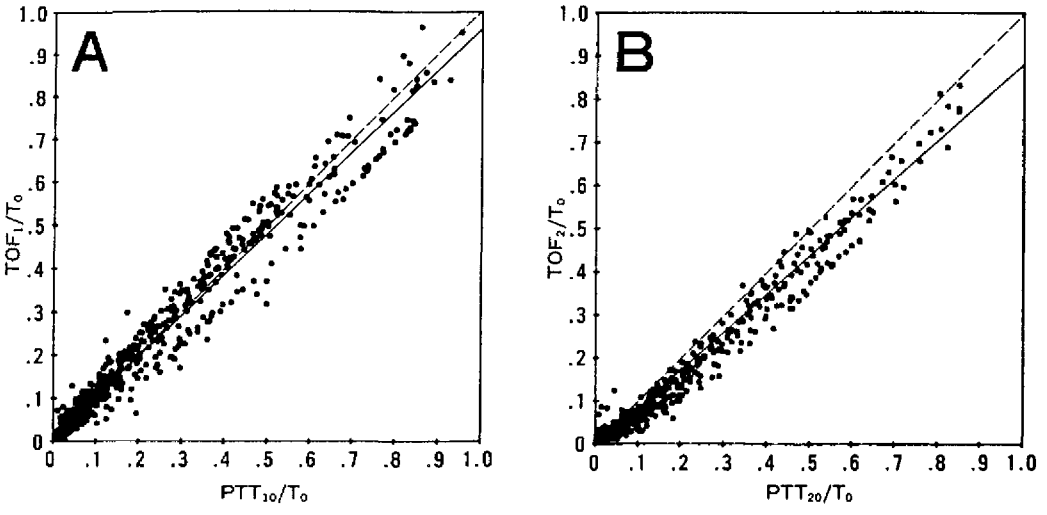

Fig. 4. Panel A(left): A relationship between the standardized magnitude of PTT_{10} and that of TOF_1 for the 579 pairs in figure 3A. The regression equation was y=0.946X ± 0.0104 (r=0.983, $P < 0.001$).

Panel B(right): A relationship between the standardized magnitude of PTT_{20} and that of TOF_2 for the 438 pairs in figure 3B. The regression equation was y=0.895X − 0.0160 (r=0.988, $P < 0.001$).

In patients who had multiple administrations of vecuronium, the PTT_i-TOF_1 and the PTT_i-TOF_2 relationships obtained after supplemental doses were not different from those obtained after initial administration of vecuronium. Figure 3A shows a mean difference between the standardized magnitude of PTT_i and that of TOF_1 obtained simultaneously. The comparison was performed in 20 patients at 579 pairs for each serial number of PTT during the period when any detectable TOF_1 was observed, either after the initial or after the supplemental administration of vecuronium, excluding data obtained after the reversal of residual curarization by neostigmine. It is to be noted that the mean magnitude of PTT_{10} was most similar to that of TOF_1. Figure 3B shows the same relationship between the magnitude of PTT_i and that of PTT_2 when any detectable TOF_2 was observed (438 pairs in 20 patients). Among the tested PTT, the mean magnitude of PTT_{20} was most similar to that of TOF_2, although there was a small but statistically significant difference between the two.

Highly significant correlation (r=0.983, $P < 0.001$) was observed between the standardized magnitude of PTT_{10} and that of TOF_1 for the 579 pairs described above (fig. 4A). The correlation between the magnitude of PTT_{20} and that of TOF_2 for the 438 pairs was also highly significant (r=0.988, $P < 0.001$), but the regression line was slightly deviated downwards from the identical line (fig. 4B).

Discussion

Our observation demonstrates that during the recovery phase from neuromuscular blockade by vecuronium under nitrous oxide and enflurane anesthesia there is a close relationship between the time of the first appearance of TOF_1 and that of PTT_1, and that once TOF_1 appeared, its magnitude is very similar to that of PTT_{10} during the whole recovery period thereafter, whether the supplemental doses of vecuronium are administered or not.

Viby-Mogensen et al.[1] reported that the time to return of response to TOF may be derived from the number of PTT responses

present, i.e. post-tetanic count (PTC). They demonstrated that, in adult patients given 0.08 mg·kg^{-1} of pancuronium, PTT_1 appeared in an average of 37 min before TOF_1. They also showed a relationship curve, in which the PTT count that coincided with the first appearance of TOF_1 was around ten. In patient with neuromuscular blockade by atracurium under nitrous oxide and halothane anesthesia, Bonsu et al.[3] reported that interval between the first appearance of PTT_1 and TOF_1 was, on an average, 9 min (95% confidence limit 4 to 14 min). They also reported that this interval increased under nitrous oxide and fentanyl anesthesia by 1 min on an average, which was not clinically significant. Gwinnutt et al.[6] reported that in pediatric patients with vecuronium (0.08 mg·kg^{-1} i.v.) under nitrous oxide and halothane anesthesia, this interval was 5.8 min, and the PTC at onset of TOF was 7.3 on an average.

The interval between the first appearance of PTT_1 and TOF_1 in our patients given vecuronium (0.2 mg·kg^{-1}) was 10 min, which was considerably shorter than that reported with pancuronium[1] and almost compatible with that reported with atracurium[3] in adult patients. This may be mainly because of the shorter duration of the neuromuscular blocking effect of vecuronium, although the absolute dose of vecuronium or concomitant use of the inhalational anesthetics, enflurane, which is believed to have potent muscle relaxation effect[8], may have had some influence on this figure. On the other hand, the PTC which coincided with the first appearance of TOF_1 in this study was almost identical to that reported in patients with pancuronium[1].

Another finding in our study, the close similarity between the magnitudes of some corresponding TOF and PTT (i.e. TOF_1 vs. PTT_{10} and TOF_2 vs. PTT_{20}) observed during the whole recovery period, has never been reported before. It is well known that neuromuscular blocking drugs have different degrees of presynaptic effect[9,10]. Since post-tetanic facilitation and fade of TOF are primarily a presynaptic phenomenon[11], the relationship between the magnitudes of PTT and TOF responses may not be uniform for all non-depolarizing neuromuscular blocking agents. The interaction between neuromuscular blocking agents and inhalational anesthetics[8,12] may also influence these relationships. Whether the relationships we observed in this study may be specific to patients under partial curarization with vecuronium or similar relationship may also be seen in patients with other non-depolarizing muscle relaxants and under different types of general anesthesia is to be clarified.

The possibility exists that relatively short interval of application of tetanic stimulation (2.5 min) may have influenced recovery of the neuromuscular transmission in the arm investigated[13]. Although we adopted this interval because of relatively rapid recovery from neuromuscular blockade by vecuronium, this problem may require further investigation.

The number of responses of PTT we observed in this study was 20, which was selected only arbitrarily. If we had observed further responses of PTT beyond 20th, it might have been able to demonstrate some more relationships between the responses to both stimulation modalities.

Although TOF response is well known as a good indicator for evaluation of light stage or residual effects of neuromuscular blockade, and PTT as a valuable method for evaluation of an intense blockade when little or no response to TOF can be obtained, relatively limited reports are available concerning the relationship between the two modalities of response. Since an integrated monitoring of wide range of neuromuscular blockade may be possible by sequentially using both modalities of response, the knowledge of relationship between these will be of great value in controlling the degree of the blockade, especially when the blockade is around the transitional phase.

The present investigation demonstrates that there is a good correlation between the responses of TOF and PTT during the neuromuscular blockade by vecuronium, and not only by observing the number of de-

tectable responses to PTT (i.e. PTC) but also by evaluating the magnitude of each response of PTT whenever this is feasible, the extent of recovery of TOF response can be predicted with a reasonable accuracy. The close relationship demonstrated between the two modalities of response will help in conducting more integrated clinical monitoring of the wide range of neuromuscular blockade during anesthesia and surgery.

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