Perioperative train-of-four monitoring and residual curarization

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It has been suggested that perioperative train-of-four (TOF) monitoring does not reduce the incidence of postoperative residual curarization (PORC). The purpose of this study was to examine whether the use of tactile assessment of the response of the adductor pollicis to supramaximal TOF stimulation of the ulnar nerve at the wrist during anaesthesia affected the incidence of PORC. Thirty-nine ASA I or II surgical patients were studied during thiopentone/fentanyl N₂O/enflurane anaesthesia. Pancuronium (70–100 µg · kg⁻¹) was used to facilitate tracheal intubation and additional pancuronium increments used to maintain surgical relaxation. The requirement for incremental doses of pancuronium and adequacy of recovery following reversal were assessed according to random allocation, either with (Group A; n = 20) or without (Group B; n = 19) access to TOF monitoring. Patients in the two groups received neostigmine in similar doses (Group A: 53 µg · kg⁻¹ (5.9); Group B: 55 µg · kg⁻¹ (5.4)). On arrival of the patient to the recovery area, neuromuscular function was assessed electromyographically (using the Datex NMT 221 to measure TOF ratio) and clinically. The incidence of PORC (TOF ratio < 70%) was greater in Group B (47%) than in Group A (15%) (P = 0.029). We conclude that the use of perioperative TOF monitoring decreases the incidence of pancuronium-induced PORC.

Key words

MONITORING,

NEUROMUSCULAR RELAXANTS: pancuronium.

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Le monitoring périopératoire du train de quatre (TOF) pourrait ne pas diminuer, selon certaines études, l'incidence de la curarisation postopératoire résiduelle (CPOR). Cette étude visait à vérifier si l'évaluation tactile de la réponse de l'adducteur du pouce à la stimulation supramaximale du nerf radial au poignet avec le TOF pendant l'anesthésie modifiait l'incidence de la CPOR. Trente-neuf patients ASA I et II ont été évalués pendant une anesthésie réalisée avec l'association thiopentone/fentanyl/N₂O/enflurane. Du pancuronium (70–100 µg · kg⁻¹) était utilisé pour permettre l'intubation et des doses subséquentes administrées pour maintenir la relaxation chirurgicale. Le besoin de doses supplémentaires de pancuronium et la qualité de la récupération après l'antagonisme ont été évalués après répartition aléatoire, soit avec (groupe A: n = 20) soit sans (groupe B: n = 19) accès au monitoring par TOF. Les patients des deux groupes ont reçu la même dose de néostigmine (groupe A: 53 µg · kg⁻¹ (5,9); groupe B: 55 µg · kg⁻¹ (5,4)). À l'admission du patient en salle de réveil, la fonction neuromusculaire a été évaluée par l'électromyographie (appareil Datex NMT 221 pour la mesure du rapport du TOF) et par la clinique. L'incidence de CPOR (rapport TOF < 70%) a été plus importante dans le groupe B (47%) que dans le groupe A (15%) (P = 0,029). Nous concluons que l'utilisation du moniteur de TOF à la période opératoire diminue l'incidence de la CPOR induite par le pancuronium.

The response to train-of-four (TOF) stimulation of a peripheral nerve is commonly used to quantify the degree of intraoperative neuromuscular blockade without prior establishment of a control response. A TOF ratio of greater than 70% correlates with criteria of adequate clinical recovery.^{1–4} Some investigators have found the incidence of postoperative residual curarization (PORC) following pancuronium administration to be unacceptably high.⁵ In very different clinical settings, the incidence of PORC after the use of pancuronium is consistently greater than that after vecuronium or atracurium.^{6–12} Potential solutions to this problem include avoiding the use of pancuronium for cases in which immediate postoperative tracheal extubation is planned, or meticulous monitoring of the effects of reversal of neuromuscular blockade. However, it has been suggested that perioperative neuromuscular monitoring is not useful in reducing the

incidence of PORC.¹³ The data on which this conclusion was based are surprising¹⁴ and the role of TOF monitoring in the prevention of PORC warrants re-examination. The current study examined the influence of manual TOF assessment on the frequency and degree of PORC, following intraoperative administration of pancuronium and maintenance of anaesthesia with nitrous oxide, enflurane and fentanyl.

Methods

With approval of the Institutional Human Studies Committee, and having obtained written informed consent from each, 39 adult ASA I or II patients, scheduled to undergo elective abdominal surgical procedures requiring profound muscle relaxation, were studied. They were free from neuromuscular disease and were receiving no medication known to influence neuromuscular function.

The anaesthetists who participated in the study were experienced with the use of pancuronium and the maintenance of muscle relaxation both with and without access to a peripheral nerve stimulator (Constant Current Peripheral Nerve Stimulator, Fisher and Paykel, Medical Auckland, New Zealand, model A400). Following diazepam pre-medication, anaesthesia was induced with thiopentone ($4-6 \text{ mg} \cdot \text{kg}^{-1}$) and fentanyl ($4-8 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) and maintained with 66% nitrous oxide in oxygen, enflurane (inspired concentration $<0.75\%$), and increments of fentanyl or thiopentone as clinically indicated. Both upper limbs were covered with blankets to maintain peripheral temperature during the procedure. Pancuronium ($70-100 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) was used to facilitate tracheal intubation. No attempt was made to titrate the initial (intubating) dose of pancuronium to neuromuscular blocking effect using the peripheral nerve stimulator. According to a random allocation, further increments of pancuronium were administered based either on the response to TOF stimulation and clinical criteria (Group A; $n = 20$) or by clinical criteria alone (Group B; $n = 19$). Participating anaesthetists in Group A attempted to maintain a degree of muscle relaxation such that one or two adductive responses of the thumb were detectable by tactile evaluation in response to TOF stimulation of the ulnar nerve at the wrist using cutaneous electrodes. In Group B, participating anaesthetists chose the dose and timing of pancuronium increments based on clinical factors such as spontaneous muscle movement, spontaneous respiratory effort or surgical satisfaction with the degree of relaxation of the abdominal wall. After completion of the surgical procedure, neostigmine and atropine or glycopyrrolate were administered to all patients. The timing and dose of administration of reversal drugs were chosen by the participating anaesthetists. Adequacy of reversal was assessed in Group A patients using TOF monitoring and

clinical judgement (based on clinical signs such as sustained head lift, hand grip strength, and eye-opening to command), and in Group B patients during clinical criteria alone.

On arrival in the recovery room, approximately 20 min after reversal of NMB, an investigator who was unaware of the group to which the patient belonged, assessed recovery of neuromuscular function both electromyographically and clinically. A Datex NMT 221 Relaxograph in the uncalibrated mode was used to quantify the integrated electromyographic response to supramaximal TOF stimulation of the ulnar nerve. The percutaneous sensing electrodes were placed over the belly of the first dorsal interosseous muscle of the hand and its insertion into the base of the proximal phalanx of the index finger. A TOF ratio of less than 70% was considered inadequate. The clinical tests used were sustained head lift for five seconds, and adequacy of cough and hand grip. If a patient, who was awake enough to co-operate, was unable to perform one or more of these tests, he or she was judged to be inadequately clinically recovered. The groups were compared for frequency and degree of PORC based on these criteria. The following data were retrieved from the anaesthesia record and tabulated:

- 1 The duration of the procedure (the interval from induction of anaesthesia until extubation).
- 2 The total dose of pancuronium used.
- 3 The dose of pancuronium administered as supplemental increments i.e., the total dose minus the dose used for intubation.

Participating anaesthetists were not directed to give a specific dose of neostigmine nor to administer supplemental neostigmine if certain criteria were not met. The dose of neostigmine administered in the two groups were compared retrospectively from examination of the anaesthetic records.

Minimum sample size (19/group) was calculated based on: $\alpha = 0.05$; $\beta = 0.20$; and a standardized effect size (0.79) calculated from historical data (mean postoperative TOF ratio following pancuronium = 74.4% (18.6); reference 6). Data were analysed using unpaired Student's *t* test, and the Chi-squared test. $P < 0.05$ was considered significant.

Results

Groups A and B were similar in terms of age, weight and duration of procedure (Table I). Only one male patient was studied in each of the two groups. The tracheas of all patients were extubated prior to transfer to the recovery room. All 39 patients studied had recovered sufficiently from the effects of their anaesthetic to cooperate by attempting to perform the clinical tests. No differences were present between the two groups in terms of total

TABLE I Age, weight and procedure duration

Group	Age (yr)	Weight (kg)	Duration (min)
A (n = 20)	42.4 (11.2)	64.8 (13.0)	179 (66.6)
B (n = 19)	44.1 (14.8)	61.1 (9.2)	149 (57.6)

Data are mean (SD).

($P = 0.42$) or incremental ($P = 0.78$) doses of pancuronium or the ratio of either of these two variables to duration of the procedure ($P = 0.25$ and $P = 0.93$ respectively) (Table II). The doses of neostigmine administered to patients in the two groups were similar (Group A: mean = $53 \mu\text{g} \cdot \text{kg}^{-1}$ (SD = 5.9); Group B: mean = $55 \mu\text{g} \cdot \text{kg}^{-1}$ (SD = 5.4)). In each case, the total dose of neostigmine was administered as a single bolus dose. As summarised in Table III, the mean TOF ratio in the recovery room was less in Group B (0.72) than in Group A (0.88) ($P = 0.039$). The incidence of PORC, as defined by a TOF ratio of 70% or less, was greater in Group B (47%) than Group A (15%) ($P = 0.029$). The incidence of PORC as defined by clinical criteria was mathematically but not statistically greater in Group B (3/19; 16%) than in Group A (1/20; 5%).

Discussion

Under the conditions described, intraoperative tactile evaluation of the response to TOF stimulation reduced the incidence and degree of PORC following pancuronium-induced NMB.

Bevan *et al.*⁶ attempted to identify factors which caused or contributed to PORC. Twenty-four of the 150 patients studied were found to have TOF ratios of less than 70%; neuromuscular monitoring had been used intraoperatively in 22 of these. The authors state that use of a peripheral nerve stimulator had been noted in 74% of all patients. These data imply that 20% (22/111) of monitored patients had TOF ratio <70%, compared with 5% (2/39) of non-monitored patients. Of course, a comparison of these two proportions (20% vs 5%) cannot be used to draw a conclusion since the distribution of other relevant factors, such as the use of pancuronium or of an inhalational agent between the monitored and non-monitored groups, is not provided. The frequency with which neuromuscular monitoring techniques were used was not determined. Thus, it is not possible from this study to conclude whether or not intraoperative neuromuscular monitoring is beneficial in terms of PORC.

Tactile evaluation of the response to TOF stimulation was used intraoperatively in all 30 patients studied by Hutton *et al.*⁷ Reversal of pancuronium- or atracurium-induced NMB was attempted only when the third component of the response was just palpable. Despite this

TABLE II Total (T) and incremental (I) doses of pancuronium relative to procedure duration (Dur)

Group	T (mg)	I (mg)	T/Dur ($\text{mg} \cdot \text{min}^{-1}$)	I/Dur ($\text{mg} \cdot \text{min}^{-1}$)
A (n = 20)	6.78 (1.6)	1.45 (1.0)	0.041 (0.009)	0.008 (0.005)
B (n = 19)	6.33 (1.8)	1.34 (1.4)	0.046 (0.013)	0.009 (0.009)

Data are mean (SD).

TABLE III TOF ratios, and proportions of patients with TOF ratio <0.7 and with adequate clinical recovery (ACR)

Group	TOF ratio (%) mean (SD)	Proportion of patients with TOF < 70% (%)	Proportion of patients with ACR (%)
A	88.6 (17.9)*	15*	95
B	71.5 (28.0)	47*	84

Data for TOF ratio are mean (SD).

* $P < 0.05$.

careful monitoring, substantial deficits in hand grip strength and expiratory force were detectable at 30 min after reversal in the patients who had received pancuronium (and to a lesser extent in those who had received atracurium).

Pedersen *et al.*¹³ performed a randomized, prospective clinical trial on 80 patients to investigate whether perioperative tactile evaluation of the TOF response was useful in reducing the incidence of PORC. The authors concluded that the use of a peripheral nerve stimulator had no effect on the total dose of muscle relaxant administered, on the need for supplementary doses of anticholinesterase in the recovery room, on the time from the end of surgery to the end of anaesthesia, or on the incidence of PORC. The following considerations¹⁴ are relevant in interpreting these surprising conclusions:

- 1 A non-volatile anaesthetic technique was used for maintenance, and so the risk of potentiation of the NMB by an inhalational agent was not present.
- 2 Low doses of muscle relaxant were used relative to the duration of the procedures. For instance, in the pancuronium monitored group, pancuronium (mean dose = 8 mg) was used for gastrointestinal procedures lasting 200 min (mean duration).
- 3 The participating anaesthetists were instructed not to attempt reversal until evidence of spontaneous recovery was present; at least one and preferably two responses to TOF stimulation in the monitored group or spontaneous skeletal muscle activity in the non-monitored group.
- 4 All patients received at least 2.5 mg neostigmine and if this was deemed inadequate, a further 2.5 mg was permissible.

5 All the patients studied had to be capable of sustaining a five-second head lift before discharge to the recovery room. This criterion is difficult to reconcile with the fact that ten patients were subsequently unable to sustain a five-second head lift in the recovery room.

Despite the strict criteria described above and the 10–33 min interval from the end of surgery until the end of anaesthesia, 35 patients (43%) had a TOF ratio of <70% in the recovery room. Seventeen patients required supplementary reversal. Even taking into account the possibility of inaccurate clinical assessment, faulty monitoring techniques, peripheral cooling or over-reversal (neostigmine-induced block) these data are difficult to explain.

The current study indicates that the use of intraoperative TOF monitoring reduces, but does not eliminate, the frequency of PORC. Detection of incomplete reversal of neuromuscular blockade using this technique may be difficult. Tactile evaluation of a TOF ratio between 0.41–0.7 is associated with a great likelihood of failure to detect fade, even when the evaluator is experienced with this monitoring technique.¹⁵ When the TOF ratio is greater than 0.4, more instances of fade are detectable with double burst (DBS) than with TOF stimulation.¹⁶ To date DBS and TOF stimulation have not been compared in terms of frequency or degree of PORC.

In this study, adequacy of neuromuscular function in the recovery room was assessed using clinical tests and EMG. Reversal of neuromuscular blockade was judged to be inadequate in 12 patients by EMG, and only four by clinical assessment. This discrepancy may be attributable to shortcomings of the EMG as a means of quantifying neuromuscular function or to the threshold TOF ratio (0.7) used as indicative of adequate neuromuscular function. There is usually good correlation between EMG activity and the force of contraction in response to nerve stimulation.^{17,18} However, EMG activity is less influenced by initial muscle fibre length and frequency of nerve stimulation.¹⁹ In general, after administration of non-depolarizing muscle relaxants, EMG response is depressed more slowly and recovers more rapidly than does the measured force of contraction.¹⁹ Thus, the use of EMG in this setting would tend to underestimate the true incidence of PORC. A TOF ratio of 0.7 has been found to be an insensitive test for residual weakness as defined by failure to sustain headlift.⁶ Clinical tests were useful in recognizing only six of 18 awake patients with TOF < 0.7 (measured by mechanomyography in the recovery room).⁶ Alternative thresholds suggested have ranged from 0.5²⁰–0.9.⁶ Our choice of this value is based on the correlation that exists between the quantified response to TOF stimulation and clinical recovery of neuromuscular function in healthy anaesthetised patients,¹ non-

medicated conscious volunteers,² and patients of ASA classes III and IV following major surgery.³

An intrinsic difficulty exists in attempting to determine the frequency of a potentially detrimental event that may otherwise pass unidentified. The very attempt to study it tends to heighten the participants' awareness of the problem and they may be more cautious in this regard than usual. One approach (which we have employed in this study) is to unblind the participating anaesthetists and to interpret the results as those of "best effort."

The use of long-acting non-depolarizing muscle relaxants is associated with a greater incidence of PORC than when intermediate-acting agents are used.^{6–12} The data presented here support previous findings that the intraoperative use of pancuronium is associated with a high frequency of PORC,^{6–9} whether neuromuscular monitoring is employed or not. The objective of this study was not to estimate the incidence of PORC in current clinical anaesthetic practice; it was to quantify the effect, if any, of the use of one neuromuscular monitoring technique on the incidence and degree of PORC. Pancuronium was chosen as the muscle relaxant, because it is widely used in clinical practice and the likelihood of demonstrating such an effect, if it is present, is greater when a long-acting agent is used.

The total and incremental doses of pancuronium used, relative to the duration of the procedure were similar in the monitored and non-monitored groups. Patients in both groups received pancuronium 70–100 $\mu\text{g} \cdot \text{kg}^{-1}$ as an initial dose and a small number of increments (0.5 or 1 mg each). The similarity of the total doses of pancuronium used in the two groups is not unexpected because the incremental dose comprises only a small proportion of each patient's total dose. The similarity in the incremental doses in the two groups may be due to the small number (usually one or two) of increments administered to each patient. Alternatively, it might be argued that anaesthetists in Group B (in the absence of an accurate monitor for titration) are equally likely to administer too much as too little muscle relaxant. Thus the incremental doses administered in Group B will be equally likely to be greater than or less than the optimal dose, i.e., that required to maintain one or two twitches in response to TOF stimulation. Because of inter-patient variability in response to muscle relaxants, it is possible that TOF monitoring could be used to titrate the initial (intubating) dose to effect, reducing the total dose administered to some patients. The well-documented differences in potency and speed of onset of non-depolarizing muscle relaxants at the hand and the laryngeal muscles would have to be taken into account if adductor pollicis monitoring were used for this purpose.²¹ In this study, routine clinical practice was sim-

ulated by administration of a commonly used dose range of pancuronium ($70\text{--}100\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) in order to examine specifically the effects of TOF monitoring on subsequent management of muscle relaxation and reversal.

In summary, this study indicates that the use of perioperative TOF monitoring reduces PORC in incidence and degree. Since the participating anaesthetists in this study were experienced in the use of TOF monitoring and since the muscle relaxant used, pancuronium, is associated with a high incidence of PORC, it will be necessary to test this conclusion in other clinical settings.

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References

- 1 Ali HH, Kitz RJ. Evaluation of recovery from non-depolarizing neuromuscular block, using a digital neuromuscular transmission analyser: preliminary report. *Anesth Analg* 1973; 52: 740–5.
- 2 Ali HH, Wilson RS, Savarese JJ, Kitz RJ. The effect of tubocurarine on directly elicited train-of-four muscle response and respiratory measurements in humans. *Br J Anaesth* 1975; 47: 570–3.
- 3 Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses. *Anesth Analg* 1977; 56: 55–8.
- 4 Shorten GD. Postoperative residual curarization: incidence, aetiology and associated morbidity. *Anaesth Intensive Care* 1993; 21: 782–9.
- 5 Viby-Mogensen J, Jørgensen BC, Ørding H. Residual curarization in the recovery room. *Anesthesiology* 1979; 50: 539–41.
- 6 Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade; a comparison between atracurium, vecuronium, and pancuronium. *Anesthesiology* 1988; 69: 272–6.
- 7 Hutton P, Burchett KR, Madden AP. Comparison of recovery after neuromuscular blockade by atracurium or pancuronium. *Br J Anaesth* 1988; 60: 36–42.
- 8 Andersen BN, Madsen JV, Schurizek BA, Juhl B. Residual curarization: a comparative study of atracurium and pancuronium. *Acta Anaesthesiol Scand* 1988; 32: 79–81.
- 9 Jensen E, Engebaek J, Andersen BN, *et al.* The frequency of residual neuromuscular blockade following atracurium (A), vecuronium (V) and pancuronium (P). A multicentre randomized study. *Anesthesiology* 1990; 73: A914.
- 10 Kong KL, Cooper GM. Recovery of neuromuscular function and postoperative morbidity following blockade by atracurium, alcuronium and vecuronium. *Anaesthesia* 1988; 43: 450–3.
- 11 Collins KM, Plantevin OM, Docherty PW. Comparison of atracurium and alcuronium in day-case gynaecological surgery. *Anaesthesia* 1984; 39: 1130–4.
- 12 Fragen J, Shanks CA. Neuromuscular recovery after laparoscopy. *Anesth Analg* 1984; 63: 51–4.
- 13 Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engbaek J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? *Anesthesiology* 1990; 73: 835–9.
- 14 Ali HH, Shorten G. Nerve stimulation and residual neuromuscular block (Letter). 1991; 74: 956–7.
- 15 Viby-Mogensen J, Jensen NH, Engbaek J, Ørding H, Skovgaard LT, Chraemmer-Jørgensen B. Tactile and visual evaluation of the response to Train-of-Four nerve stimulation. *Anesthesiology* 1985; 63: 440–3.
- 16 Engbaek J, Østergaard D, Viby-Mogensen J. Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block. *Br J Anaesth* 1989; 62: 274–8.
- 17 Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block (Part I). *Br J Anaesth* 1971; 43: 473–6.
- 18 Kopman AF. The relationship of evoked electromyographic and mechanical responses following atracurium in humans. *Anesthesiology* 1985; 63: 208–11.
- 19 Harper NJN. Neuromuscular blockade; measurement and monitoring. In: BJ Pollard (Ed.). *Applied Neuromuscular Pharmacology*. Oxford, New York, Tokyo: Oxford University Press, 1994; 336–7.
- 20 Jones RM, Pearce AC, Williams JP. Recovery characteristics following antagonism of atracurium with neostigmine and edrophonium. *Br J Anaesth* 1984; 56: 453–7.
- 21 Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. *Anesthesiology* 1991; 74: 833–7.