Hand or foot train-of-four tests and surgical site muscle relaxation assessed with multiple motor evoked potentials: A prospective observational study

Betz, Michael ; Aguirre, José ; Schubert, Martin ; Götschi, Tobias ; Huber, Barbara ; Schüpbach, Regula ; Brada, Muriel ; Spirig, José M ; Farshad, Mazda

Abstract: BACKGROUND Intra-operative muscle relaxation is often required in orthopaedic surgery and the hand train-of-four (TOF) test is usually used for its quantification. However, even though full muscle relaxation is claimed by anaesthesiologists based on a TOF count of zero, surgeons observe residual muscle activity. OBJECTIVE The aim of the study was to assess if hand or foot TOF adequately represents intra-operative muscle relaxation compared with multiple motor evoked potentials. DESIGN Prospective observational study. SETTING A single-centre study performed between February 2016 and December 2018 at the Balgrist University Hospital, Zurich, Switzerland. PATIENTS Twenty patients scheduled for elective lumbar spinal fusion were prospectively enrolled in this study after giving written informed consent. INTERVENTIONS To assess neuromuscular blockade (NMB) with the intermediate duration nondepolarising neuromuscular blocking agent rocuronium, hand TOF (adductor pollicis) and foot TOF (flexor hallucis brevis) monitoring, and muscle motor evoked potentials (MMEPs) from the upper and lower extremities were assessed prior to surgery under general anaesthesia. Following baseline measurements, muscle relaxation was performed with rocuronium until the spinal surgeon observed sufficient relaxation for surgical intervention. At this timepoint, NMB was assessed by TOF and MMEP. MAIN OUTCOME MEASURES The primary outcome was to determine the different effect of rocuronium on muscle relaxation comparing hand and foot TOF with the paraspinal musculature assessed by MMEP. RESULTS Hand TOF was more resistant to NMB and had a shorter recovery time than foot TOF. When comparing MMEPs, muscle relaxation occurred first in the hip abductors, and the paraspinal and deltoid muscles. The most resistant muscle to NMB was the abductor digiti minimi. Direct comparison showed that repetitive MMEPs simultaneously recorded from various muscles at the upper and lower extremities and from paraspinal muscles reflect muscle relaxation similar to TOF testing. CONCLUSION Hand TOF is superior to foot TOF in assessing muscle relaxation during spinal surgery. Hand TOF adequately represents the degree of muscle relaxation not only for the paraspinal muscles but also for all orthopaedic surgical sites where NMB is crucial for good surgical conditions. TRIAL REGISTRATION clinicalTrials.gov (NCT03318718).

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Michael Betz*, José Aguirre*, Martin Schubert, Tobias Götschi, Barbara Huber, Regula Schüpbach, Muriel Brada, José M. Spirig and Mazda Farshad

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MAIN OUTCOME MEASURES The primary outcome was to determine the different effect of rocuronium on muscle relaxation comparing hand and foot TOF with the paraspinal musculature assessed by MMEP.

RESULTS Hand TOF was more resistant to NMB and had a shorter recovery time than foot TOF. When comparing MMEPs, muscle relaxation occurred first in the hip abductors, and the paraspinal and deltoid muscles. The most resistant muscle to NMB was the abductor digiti minimi. Direct comparison showed that repetitive MMEPs simultaneously recorded from various muscles at the upper and lower extremities and from paraspinal muscles reflect muscle relaxation similar to TOF testing.

CONCLUSION Hand TOF is superior to foot TOF in assessing muscle relaxation during spinal surgery. Hand TOF adequately represents the degree of muscle relaxation not only for the paraspinal muscles but also for all orthopaedic surgical sites where NMB is crucial for good surgical conditions.

TRIAL REGISTRATION clinicalTrials.gov (NCT03318718).

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Introduction

Intra-operative muscle relaxation is of pivotal importance for visualisation of deep structures during a surgical exposure in orthopaedic surgery. For different surgical disciplines, insufficient muscle relaxation was observed in more than a quarter of patients and associated with poor intra-operative conditions.[1–3] In anaesthesia, neuromuscular blocking agents (NMBAs) are used not only to facilitate tracheal intubation but also to improve

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surgical conditions.[4,5] Moreover, for spinal surgery, deep neuromuscular blockade (NMB) has been shown to reduce intra-operative surgical bleeding due to greater relaxation in the paraspinal musculature and lower intra-operative peak inspiratory pressure.[6]

NMBAs have been shown to act differently among different types of muscle. To reduce the risk of residual paralysis, quantitative monitoring using train-of-four (TOF) ratio to monitor the recovery at the adductor pollicis muscle has been introduced.[7,8] However, some surgical procedures, such as cervical spine surgery and neurosurgical procedures, do not allow easy access to the hand for acceleromyographic monitoring. Electrical stimulation of the posterior tibial nerve leading to contractions of the flexor hallucis brevis muscle has been introduced into clinical practice with studies comparing the time courses of NMBAs at the adductor pollicis and flexor hallucis brevis muscles.[9,10] These studies have shown that a time lag of muscle recovery from NMB can occur between muscles of the upper and lower extremities. Therefore, a TOF test performed on the lower extremity muscles can show full recovery, but at the same time, some muscles of the upper extremity and the paraspinal musculature could show incomplete recovery, or vice versa.[11]

This reinforces the subjective feeling of the surgeons about remaining muscle activity despite a TOF value of zero. Gavrancic *et al.*[9] observed a significant difference between T1 to T4 decrements obtained from intrinsic hand and foot muscles ($P < 0.05$). The T1 to T4 decrement determined from the abductor hallucis muscle in their study was indicating less relaxation effect and more rapid recovery than in the first dorsal interosseous muscle of the hand ($P < 0.05$). These results suggest that hand TOF might underestimate muscle relaxation in other muscle groups of the body.

Another possible method to quantify muscle relaxation is the assessment of repetitive muscle motor evoked potentials (MMEPs), which are commonly used during spinal surgery for neuromonitoring of integrity of the motor pathway from the cortical level to the muscle.[12,13] Since MMEPs are elicited by repetitive transcranial electric stimulation over the scalp and can simultaneously be recorded from various muscles in the upper and lower extremities and from paraspinal muscles, they may provide more information about the anatomical distribution of the relaxation effect in different muscle groups than TOF tests.

By comparing both monitoring methods, TOF and MMEPs, simultaneously during stepwise muscle relaxations, we aimed to determine if TOF of intrinsic hand and foot muscles is sufficient to assess intra-operative muscle relaxation in paraspinal muscles and various muscles of the upper and lower extremities. Further, we investigated in which sequence different muscles respond to, and recover from, muscle relaxation.

Table 1 Demographics

Patient	Age	Sex	Weight (kg)	BMI (kg m^{-2})
1	51	F	80.4	28.8
2	59	F	80	34.6
3	63	M	82.9	27.7
4	44	M	80	26.7
5	73	M	93	30.7
6	79	F	55.6	21.4
7	58	F	60	22.9
8	69	F	54	20.6
9	72	M	77	26
10	70	F	53	20.2
11	67	M	82.4	29.2
12	59	M	75	25.4
13	68	M	77	27.6
14	47	F	72	24.9
15	82	F	46	18.7
16	74	F	77	28.3
17	80	M	77.9	27.9
18	80	F	52	21.6
19	29	M	102.2	30.2
20	55	F	56	18.7

Methods

The current single-centre prospective observational study was conducted between February 2016 and December 2017 at the Balgrist University Hospital, Zurich, Switzerland after obtaining the approval of the ethics committee (Kantonale Ethikkommission Zurich 2015-0462).

It was registered at ClinicalTrials.gov (NCT03318718) and conducted in accordance with the Declaration of Helsinki.[14] Informed consent was obtained from all patients before their inclusion in the study.

We included 20 patients aged 18 to 85 years, American Society of Anesthesiologists physical status 1 or 2, scheduled for elective primary lumbar spinal fusion, and with both a hand and foot available during the entire length of the scheduled elective surgery. Exclusion criteria were diabetes mellitus, neuropathy, emergency surgery, criteria suggestive of a difficult airway and history of allergy to drugs used in the study (Table 1).

Patients were premedicated with midazolam 7.5 mg and standard monitoring was applied [electrocardiography, pulse oximetry, invasive arterial blood pressure (BP), bispectral index (BIS) monitoring, TOF monitoring at the upper and lower extremities]. Anaesthesia induction was achieved with propofol and remifentanil and, to avoid interference with intra-operative neuromonitoring, maintained using target-controlled infusions (TCI) of propofol and remifentanil. To facilitate tracheal intubation and to avoid prolonged neuromuscular block prior to baseline measurement of MMEP, the short-acting depolarising NMBA succinylcholine was used intravenously in a dose of 0.6 mg kg^{-1}.[15] After fasciculation, the trachea was intubated and the lungs were ventilated mechanically (F_IO_2 0.5 in air) and the ventilator parameters were adjusted to maintain an end tidal CO_2 between 4.7 and 6.0 kPa (35 and 45 mmHg). During surgery, anaesthesia was maintained with the propofol/remifentanil TCI to achieve a BIS value between 40 and 60.[15] A bolus dose of fentanyl was given at the end of the MMEP/TOF measurements prior to extubation. The target mean arterial pressure was 70 mmHg during the whole intervention. Patient temperature was kept between 36.0 and 37.5 °C using a warming blanket system and warmed infusion solutions. Tympanic temperature was measured every 30 min.

TOF monitoring of the lower extremity consisted of supramaximal stimulation of the posterior tibial nerve using a stimulation current ranging from 30 to 60 mA adjusted to achieve supramaximal nerve stimulation. Surface stimulating electrodes were placed with the cathode over the inferoposterior aspect of the medial malleolus and the anode electrode 2 to 3 cm proximal to the cathode electrode. Surface recording electrodes placed over the belly of the flexor hallucis brevis muscle were used for TOF measurement on the foot. The stimulation current was applied at a rate of 2 Hz to deliver four contractions. The pulse duration was 0.5 ms. TOF monitoring of the upper extremity consisted of supramaximal stimulation of the ulnar nerve with current ranging from 20 to 30 mA adjusted to achieve supramaximal nerve stimulation. Surface recording electrodes placed over the belly of the adductor pollicis muscle were used for TOF measurement on the hand. A mechanosensor was placed between the thumb and first finger. The mechanosensor measured the motion of the thumb with a piezoelectric sensor. Stimulation current was applied with the same frequency and pulse duration as in the lower extremity. The same intra-operative monitoring device was used as for the lower extremity TOF (E-NMT; GE Healthcare, Helsinki, Finland). When the TOF test was performed, each of the four muscle contractions was measured and displayed. Initially, the baseline compound muscle action potential amplitude, which is the measure of the upward peak from baseline, was measured and marked, and amplitudes of four responses during TOF were automatically labelled and measured by the E-NMT programme.

MMEP monitoring was performed by neurophysiologists on an intra-operative neuromonitoring machine (Isis workstation; inomed Medizintechnik GmbH, Emmendingen, Germany). For the comparison with TOF assessment of muscle relaxation, MMEPs obtained by high-frequency multipulse transcranial electrical stimulation (TES) were elicited in trains of five monophasic, anodal, constant-current pulses of 200-μs duration (interstimulus interval 4 ms, equivalent to 250 Hz). This high-frequency multipulse stimulation is necessary to provide temporal summation to reach the firing threshold of spinal motor units.[16] Cortical stimulation sites were 2 cm lateral to the C3/C4 international electroencephalogram electrode positioning system using 100 to 180 V rectangular bipolar stimulation via transdermal scalp corkscrew needle electrodes. To compare efficacy of NMB on MMEPs with TOF peripheral nerve stimulation, a sequence of five sets of 200 Hz high-frequency TES were applied with an interstimulus interval of 0.5 s, equivalent to the 2 Hz TOF peripheral nerve stimulation. MMEPs were recorded unilaterally from the following muscles: abductor digiti minimi of the hand (ADM), deltoid, paraspinal muscles of the lumbar spine (paraspinal muscles), hip abductor (HAB), tibialis anterior, extensor hallucis longus (EHL) and abductor hallucis, using a pair of indwelling steel needle electrodes in each muscle.

Measurements of series of five 2-Hz TES-evoked MMEPs were obtained in regular intervals and compared with TOF peripheral nerve stimulation at the hand and foot to test efficacy and duration of levels of NMB.

Following baseline measurements (TOF and MMEP), muscle relaxation was performed using intra-operative bolus doses of the intermediate duration nondepolarising NMBA rocuronium 0.3 mg kg^{-1} until the spinal surgeon observed sufficient relaxation for surgical intervention (Table 2). Subsequently, the same MMEPs were compared with TOF in terms of recovery from relaxation after the last dose of rocuronium. Timing of the MMEP and TOF testing was 5 min after initial and subsequent NMBA bolus doses, with regular further stimulation sequences every 10 min.

The number of MMEP responses to the sequence of 2-Hz stimulations was calculated as response number divided by stimulation number. A response was assumed present when MMEP peak-to-peak amplitude was equal to or larger than 100 μV.

At the end of surgery, neostigmine 2.5 mg and glycopyrronium bromide 0.5 mg (Robinul Neostigmine; Sintetica SA, Mendrisio, Switzerland) was administered if residual NMB was present, defined as a T4/T1 ratio less than 0.90 at the adductor pollicis. Tracheal extubation was performed after complete recovery and return of consciousness and patients were transferred to the postanaesthesia care unit.

The primary endpoint was to determine the different effect of rocuronium on muscle relaxation of the hand and foot in comparison to the paraspinal musculature. Secondary outcomes were to determine muscle relaxation in other muscles of interest for orthopaedic surgery. Further, we investigated in which sequence different muscles respond to, and recover from, muscle relaxation.

Statistical analysis

Data analysis was conducted with MATLAB (Release 2017b; The MathWorks, Inc., Natick, Massachusetts,

Table 2 **Rocuronium administration and surgical procedure**

Patient	Weight (kg)	Number of muscle relaxant doses (rocuronium 0.3 mg kg^{-1})	Timing of rocuronium doses after baseline measurement (min)	Total dose of rocuronium (mg)	Operation time (min)	Surgical procedure
1	80.4	2	5, 40	48	100	Fusion L5 to S1
2	80	3	5, 10, 15	72	195	Fusion L4 to S1
3	82.9	2	5, 10	50	150	Fusion L5 to S1
4	80	2	5, 30	48	175	Fusion L5 to S1
5	93	3	5, 10, 15	84	135	Fusion L4 to L5
6	55.6	2	5, 10	33	190	Fusion L3 to S1
7	60	2	5, 10	36	135	Fusion L4 to L5
8	54	3	5, 10, 15	49	165	Fusion L5 to S1
9	77	3	5, 10, 25	69	195	Fusion L3 to S1
10	53	4	5, 10, 15, 20	64	160	Fusion L4 to S1
11	82.4	5	5, 10, 15, 20, 35	124	240	Fusion L1 to S2/Ala
12	75	4	5, 10, 15, 20	90	195	Fusion L5 to S1
13	77	4	5, 10, 15, 20	92	150	Fusion L2 to L3
14	72	2	5, 10	43	170	Fusion L5 to S1
15	46	2	5, 10	28	160	Fusion L2 to S2/Ala
16	77	2	5, 10	46	115	Fusion L4 to L5
17	77.9	3	5, 10, 15	70	140	Fusion L4 to L5
18	52	2	5, 10	31	240	Fusion L4 to S1
19	102.2	3	5, 10, 15	92	120	Fusion L4 to L5
20	56	2	5, 10	34	180	Fusion L4 to S1

USA) and SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York, USA). Time to relaxation was computed for each muscle. For inference testing, cases without complete relaxation were imputed with response time 100 s. Time to relaxation was defined as the time from T0 until the relaxation was complete for the first time (TOF or MMEP = 0), irrespective of potential additional anaesthetics. If more than three measurements for one patient and muscle were missing and relaxation was not reached, the data were excluded. For muscle and TOF recovery, for each subject and muscle, time 0 was defined as first time at minimum muscle/TOF twitches.

To compare relaxation time of the different muscles, a Friedman's test was employed.

Sensitivity and specificity of hand TOF and foot TOF in detecting complete relaxation were calculated for each muscle separately as well as for the set of all assessed muscles. The frequencies of false positive and false-negative predictions using hand TOF or foot TOF were compared with Fisher's exact tests. The level of significance was set at P less than 0.05.

Results

All patients were kept at the desired temperature range (36.0 to 37.5 °C) throughout the surgical intervention.

Train-of-four sensitivity and specificity

Sensitivity and specificity of hand TOF and foot TOF for full muscle relaxation are shown in Table 3. As an example, the first column for ADM shows that when the hand TOF was zero, MMEPs for ADM were not detectable in 65% of all measurements; consequently, hand TOF sensitivity for ADM was 0.65. When the hand TOF was not zero, MMEPs for ADM were not zero in 70% of all measurements; consequently, hand TOF specificity for ADM was 0.7.

Train-of-four and muscle motor evoked potentials

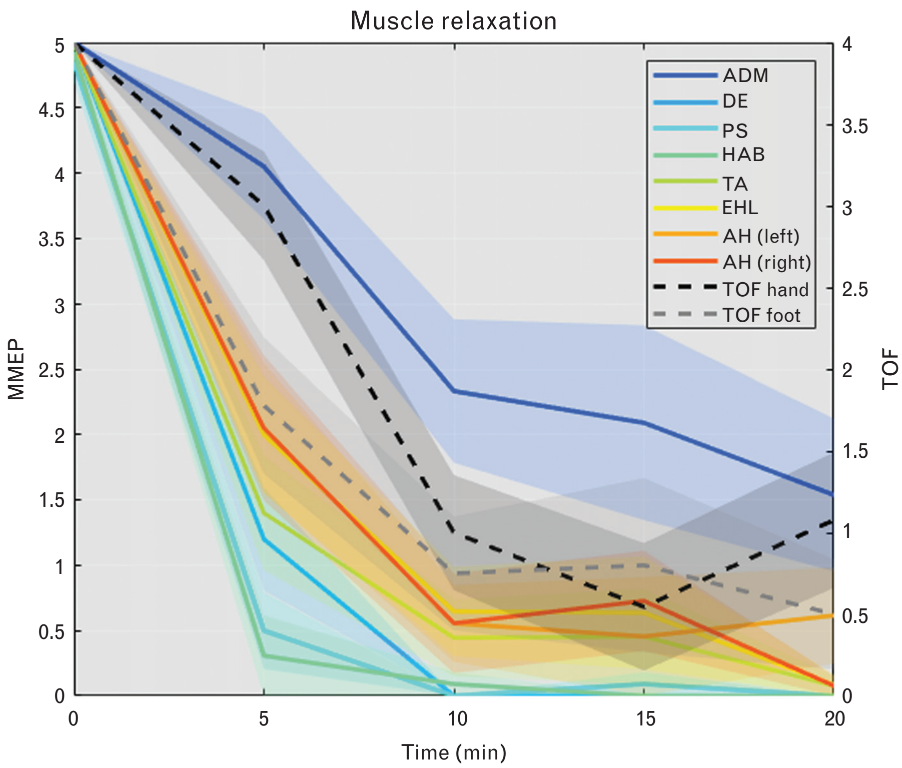
When no twitches were present in the hand TOF (TOF = 0), MMEPs could be detected in some cases

Table 3 **Comparison of the classification performance of the hand train-of-four with foot train-of-four in terms of their muscle-specific and overall sensitivity and specificity in predicting complete muscle relaxation**

	Assessed muscle								
TOF hand	ADM	DE	PS	HAB	TA	EHL	AH (left)	AH (right)	Overall
Sensitivity	0.65	1.00	1.00	1.00	0.95	0.89	0.85	0.90	0.90
Specificity	0.70	0.30	0.15	0.15	0.45	0.53	0.50	0.40	0.43
TOF foot									
Sensitivity	0.50	0.78	0.94	0.91	0.67	0.59	0.67	0.89	0.74
Specificity	0.94	0.56	0.50	0.64	0.50	0.71	0.72	0.61	0.66
Comparison									
P value, sensitivity	0.512	0.041	0.474	0.458	0.038	0.055	0.26	1	<0.001
P value, specificity	0.093	0.188	0.035	0.033	1	0.322	0.198	0.33	<0.001

ADM, abductor digiti minimi of the hand; AH, abductor hallucis; DE, deltoid; EHL, extensor hallucis longus; HAB, hip abductors; PS, paraspinal muscles; TA, tibialis anterior; TOF, train-of-four.

Fig. 1 Time to relaxation of each muscle assessed by muscle motor evoked potentials, hand train-of-four and foot train-of-four following administration of rocuronium



Coloured lines join mean values at each time point, coloured fields represent the SEM. ADM, abductor digiti minimi of the hand; AH, abductor hallucis; DE, deltoid; EHL, extensor hallucis longus; HAB, hip abductors; MMEP, muscle motor evoked potentials; PS, paraspinal muscles; TA, tibialis anterior; TOF, train-of-four.

for ADM (n=7), abductor hallucis (n=5), EHL (n=2) and tibialis anterior (n=1). However, in 90% of all measurements (n=137) no MMEPs could be detected as soon as hand TOF was zero. In the deltoid, paraspinal muscles and HAB, MMEPs were not detectable in any patient as soon as the hand TOF was 0. Therefore, hand TOF sensitivity for deltoid, paraspinal muscles and HAB MMEPs was 1.00 (Table 3). However, the specificity of hand TOF for MMEPs of these muscles was low (0.3, 0.15, 0.15) (Table 3). That means that even when hand TOF was not zero, MMEPs could not be detected in most measurements of these muscles (MMEPs = 0 in 70% of deltoid, 85% in paraspinal and HABs). This is due to the fact that TOF in the hand was much more resistant to muscle relaxation than deltoid, paraspinal muscles and HAB muscles represented by MMEP testing (Fig. 1).

When no twitches were observed in the foot TOF (TOF = 0), MMEPs could be detected in ADM (n=9), deltoid (n=4), paraspinal muscles (n=1), HAB (n=1), tibialis anterior (n=6), EHL (n=7) and abductor hallucis (n=8). Accordingly, foot TOF was inferior to hand TOF in terms of detection of insufficient muscle relaxation, resulting in a lower sensitivity but higher specificity for foot TOF (Table 3).

Time to relaxation

The time to relaxation of each tested muscle in terms of MMEPs as well as hand TOF and foot TOF response following rocuronium administration are shown in Fig. 1. Friedman's test revealed a significant difference in terms of time to relaxation for the different muscles tested [$\chi^2(7) = 37.975$, $P < 0.001$]. The most resistant muscles to NMBA blockade in MMEP testing were ADM > EHL > abductor hallucis > tibialis anterior > deltoid > paraspinal muscles > HAB.

Hand TOF was more resistant than foot TOF. The mean times to relaxation of each tested muscle are shown in Table 4.

Recovery

Recovery of muscle activity as well as hand TOF and foot TOF after the last dose of rocuronium is shown in Fig. 2. The order of recovery of muscle response as tested by MMEP was: ADM > tibialis anterior > abductor

Table 4 Time to relaxation of each tested muscle and hand/foot train-of-four

Assessed muscle	Time to relaxation (min)
ADM	10 (5 to 30)
DE	5 (5 to 10)
PS	5 (5 to 10)
HAB	5 (5 to 15)
TA	5 (5 to 40)
EHL	10 (5 to 40)
AH (left)	5 (5 to 15)
AH (right)	5 (5 to 25)
Hand TOF	10 (5 to 40)
Foot TOF	10 (5 to 30)

Values are median (range). ADM, abductor digiti minimi of the hand; AH, abductor hallucis; DE, deltoid; EHL, extensor hallucis longus; HAB, hip abductors; MMEP, muscle motor evoked potentials; PS, paraspinal muscles; TA, tibialis anterior; TOF, train-of-four.

hallucis = EHL > paraspinal muscles > deltoid > HAB. Hand TOF recovered faster than foot TOF.

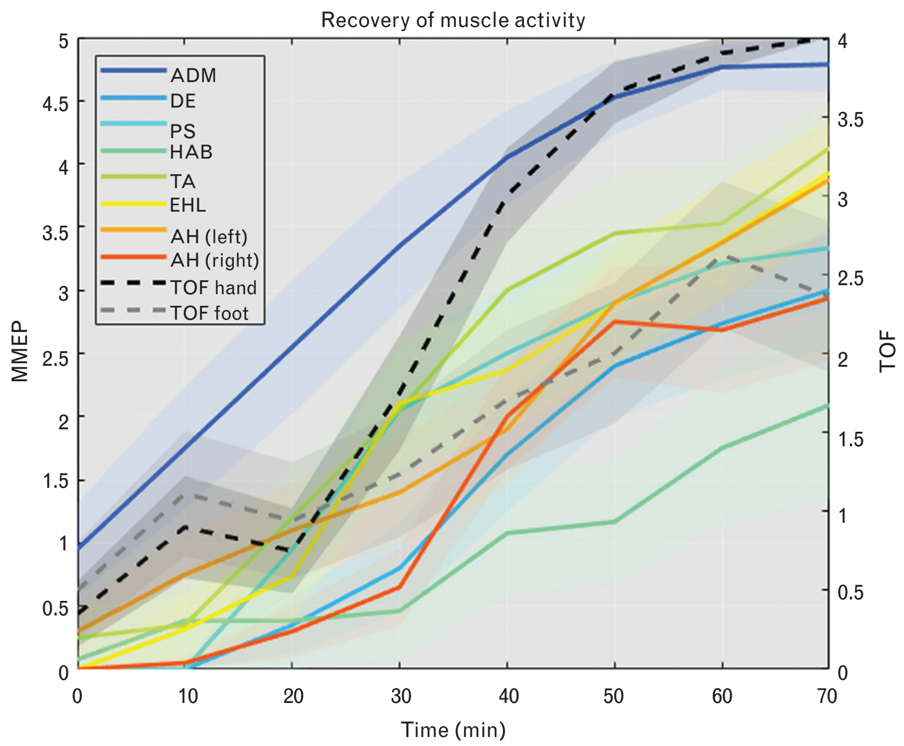
Discussion

By direct comparison of relaxation assessment obtained either by means of TOF at the hand and foot or with TES-induced MMEP recordings of several muscle groups including paraspinal muscles, we aimed to find whether hand TOF was sufficient to assess intra-operative muscle relaxation and in which sequence different muscles respond to, and recover from, muscle relaxation.

This comparison showed that TOF testing reflects muscle relaxation similar to repetitive MMEP simultaneously recorded from various muscles at the upper and lower extremities and from paraspinal muscles.

First, it could be clearly documented that onset of relaxation of muscles in the upper and lower extremities followed a systematic order in which most proximal muscles would be relaxed first, followed by more distal muscles and upper extremity muscles following those of the lower extremity. Conversely, recovery from relaxation followed the opposite order. From these results it can be concluded that TOF at the hand was a good method of assessing intra-operative muscle relaxation with respect to more proximal muscles such as hip, shoulder and paraspinal muscles. When no twitches were present in hand TOF (TOF = 0), MMEPs were not detectable in 90% of all MMEP measurements. In the deltoid, paraspinal muscles and HABs, MMEPs were not detectable in any patient as soon as hand TOF was zero. As a consequence, insufficient muscle relaxation seems to be very unlikely in shoulder, spine and hip surgery when hand TOF is zero. MMEPs in the ADM, abductor hallucis, EHL and tibialis anterior were still detectable

Fig. 2 Time to recovery of muscle activity assessed by muscle motor evoked potentials, hand train-of-four and foot train-of-four



Coloured lines join mean values at each time point, coloured fields represent the SEM. ADM, abductor digiti minimi of the hand; AH, abductor hallucis; DE, deltoid; EHL, extensor hallucis longus; HAB, hip abductors; MMEP, muscle motor evoked potentials; PS, paraspinal muscles; TA, tibialis anterior; TOF, train-of-four.

in some cases even though hand TOF was zero. However, full muscle relaxation is less frequently required in hand and foot surgery for adequate intra-operative anatomical exposure.

The use of NMBA for general anaesthesia can lead to important side effects such as residual paralysis with consequent delayed recovery from general anaesthesia. To avoid these complications, many operations are performed avoiding the use of a NMBA. Li *et al.*[15] showed in a prospective randomised study on 86 adults who underwent elective spinal surgery that general anaesthesia without a NMBA provided similar surgical conditions to those observed with a NMBA. Moreover, avoidance of NMBAs was associated with earlier eye opening, extubation and a higher level of consciousness on emergence from spinal surgery. However, in that study, only 23% of operations included spinal fusion which demands different surgical conditions compared with simple decompression. Kang *et al.*[6] found in a study on 88 patients who underwent posterior lumbar interbody fusion (two-level or three-level) that deep NMB reduced intra-operative surgical bleeding due to greater relaxation in the paraspinal musculature.

Concerning detection of insufficient muscle relaxation, we found that sensitivity of hand TOF is superior to foot TOF (Table 3). Hand TOF was more resistant to NMBA than foot TOF (Fig. 1). Furthermore, hand TOF recovered earlier than foot TOF after the last dose of NMBA (Fig. 2). Consequently, there is no relevant gain of information by including foot TOF for the assessment of muscle relaxation in orthopaedic surgery. This finding is not in agreement with published data of Gavrancic *et al.*,[9] who found a shorter recovery of foot TOF compared with hand TOF, which led these authors to recommend inclusion of foot TOF in addition to hand TOF to assess NMB during spinal surgery. However, there are methodological differences with respect to hand TOF.[17] The classical hand TOF stimulates the ulnar nerve which induces a contraction of the adductor pollicis muscle. Gavrancic *et al.*[9] stimulated the first interosseous muscle, which is not the clinical standard. Moreover, the foot TOF was also different: we stimulated the flexor hallucis brevis muscle whereas Gavrancic *et al.* stimulated the abductor hallucis muscle. There might be some differences between these different measurement points. In addition, Gavrancic *et al.* used two different NMBAs (rocuronium and cis-atracurium) and patients were divided in different groups according to different preset time points and preset doses of NMBA whereas we injected only one NMBA and repeated doses according to clinical effect. Le Merrer *et al.*[10] also showed different results comparing flexor hallucis brevis and adductor pollicis muscles TOF using atracurium and describing that the onset of NMB occurred more slowly at flexor hallucis brevis compared with adductor pollicis, whereas complete recovery occurred more quickly. However, these results were inconsistent, as valid only for 56% of the studied population. For 21% of patients, both NMB onset and recovery occurred faster at flexor hallucis brevis. These different findings might be attributed to the different NMBA used compared with our study. Moreover, the baseline TOF measurements were performed with a noncalibrated intensity of stimulation fixed at 50 mA.

We are not aware of other studies which show relevant differences of muscle relaxation induced by the NMBA rocuronium on extremity musculature in comparison with proximal muscles of shoulder and hip as well as the paraspinal muscles. The paraspinal muscles are the muscle group for which complete NMB during spinal surgery is sought to achieve the best possible surgical exposure. Since no single peripheral nerve innervates the paraspinal muscles it cannot be directly stimulated by peripheral nerve stimulation. Therefore, TOF cannot be used for direct assessment of relaxation of paraspinal muscles. In contrast, TES results in synchronised contractions of the trunk, paraspinal muscles as well as arm and leg muscles, which can be recorded as MMEPs. When relaxation is induced, MMEPs are subject to amplitude loss resulting in loss of motor response similar to TOF when repetitive 2 Hz stimuli were applied by TES. This proved to be useful to compare the effects of the NMBA on the hand and foot with that in the paraspinal musculature. The similarity of the decline of responses derived from hand TOF and hand muscle MMEP suggests that relaxation depends critically on the final common pathway of neuromuscular transmission irrespective of the notion that physiology of excitation in peripheral (TOF) and combined central and peripheral nerve (MMEP) differs substantially. We showed that paraspinal muscles were among the first muscle groups to respond to the NMBA rocuronium and among the last muscles to recover from muscle relaxation. When hand TOF was zero, MMEPs of paraspinal muscles, deltoid and HABs were not detectable in any patient.

There are some limitation of our results which require consideration. Many factors can influence the results of TOF and MMEP testing and may therefore contribute to the order of responses observed in the various muscles. Among them may be BP, temperature, oxygenation and, in the case of MMEPs (as opposed to TOF), also central nervous system excitability which is influenced by sedation and analgesia. However, we standardised the anaesthesia regimen for all these variables to reduce this bias. As MMEPs are not commonly used to asses relaxation state we had to define a cut-off value for MMEP amplitude to decide when a response was lost due to relaxation. Probably sensitivity and specificity values shown in Table 3 and the time course in Figs. 1 and 2 would change if this cut-off value is altered. However, such a change would not alter the relative response and recovery profile between MMEP muscles tested. Further the investigations of this study did focus solely on stimulated muscle activity and did not measure the tone of the muscle directly. Further studies are needed to detect whether addition of muscle relaxants would reduce the muscle tone further after the stimulated muscle activity has ceased to become measurable using standard neurophysiological quantification techniques.

With these limitations in mind, we conclude that hand TOF is a valuable measure and adequately represents the degree of muscle relaxation for most of the orthopaedic surgical sites including the paraspinal muscles.

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