Sex-related differences in the relationship between acceleromyographic adductor pollicis train-of-four ratio and clinical manifestations of residual neuromuscular block: a study in healthy volunteers during near steady-state infusion of mivacurium

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Editor’s key points
- A TOF ratio ≥0.9 equates to return of normal function after neuromuscular block (NMB).
- Study explored sex differences in TOF and clinical measures of muscle function after mivacurium.
- Males appeared to have poorer recovery of clinical function at TOF=0.9.
- This effect disappeared when TOF ratios were normalized.
- Normalized TOF should be used when assessing recovery from NMB.

Background. Studies in volunteers suggest that train-of-four (TOF) ratios >0.9 are needed to retain normal function of muscles involved in upper airway patency, swallowing, and vital capacity breathing. We determined if sex-related differences exist in the relationship between adductor pollicis (AP) TOF ratio and measures of neuromuscular function commonly used to assess recovery from neuromuscular block.

Methods. In 10 males and 10 females, three steady-state levels of neuromuscular block were achieved with mivacurium infusions. TOF ratio was measured with acceleromyography at the AP. Hand grip strength and the ability to clench the teeth, raise the head >5 s, swallow, protrude the tongue, and open the eyes were tested at each stable block level and reconciled to uncorrected and normalized (pre-paralysis values) TOF measures. These relationships were compared between sexes.

Results. The ability to clench teeth and head raise >5 s was lost at a significantly greater TOF ratio in males than females. The percentage decrease in handgrip strength with decreasing TOF ratio was proportionally greater in males than females. Forty per cent of the males were unable to clench the teeth at an uncorrected TOF ratio ≥0.9. When TOF ratios were normalized, clinical functions showed no decrement at TOF ratio ≥0.9 in any volunteer.

Conclusions. Sex-related differences exist in the relationship between AP TOF ratio and clinical measures of muscle function used to assess recovery from neuromuscular block. Normalization of AP TOF ratios is recommended because a non-normalized TOF ratio of 0.9 does not guarantee adequate reversal of neuromuscular block.

Keywords: gender; neuromuscular block, mivacurium; NM relaxant, monitoring

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Residual neuromuscular block in the postoperative period is an important clinical issue1–3 because a train-of-four (TOF) ratio <0.7 is associated with upper airway and pulmonary function-related postoperative complications.4 5 These observations are consistent with results from studies in volunteers, showing that a TOF ratio >0.9 is needed to retain normal function of muscles involved in upper airway patency, swallowing, and vital capacity breathing.6–9

There is limited information on sex-related differences in the susceptibility to adverse effects of neuromuscular blocking drugs (i.e. postoperative residual neuromuscular block), although it is known that the pharmacokinetics of these drugs differ between males and females. The volume of distribution of vecuronium and rocuronium is less in women than men, resulting in higher blood concentrations, deeper block, and prolonged duration of action in females after normal clinical doses.10 11 Therefore, in theory, females might be at greater risk than males for residual neuromuscular block in the postoperative period. However, a retrospective analysis of data in volunteers during steady-state infusions of mivacurium suggested that males are more sensitive to the effect of neuromuscular blocking drugs than females.8 The ability to perform simple functions such as clenching the teeth, swallowing, head raising >5 s, and taking a vital capacity breath appeared to be lost at a greater TOF ratio in males than females. In the present
study, we wanted to test the hypothesis that sex-related differences exist in the relationship between TOF ratio and measures of muscle function that are frequently used clinically to assess recovery from neuromuscular block.

**Methods**

This study was approved by the Institutional Review Board at the University of California, San Francisco, CA, USA. Twenty healthy volunteers: 10 males [28 (4) yr, 74 (6) kg, BMI 23 (1)] and 10 females [26 (4) yr, 58 (9) kg, BMI 21 (2)] were enrolled after an in-depth interview and written consent. Subjects were between 18 and 35 yr with a normal airway exam. Subjects who were pregnant or currently breastfeeding, had a BMI >25, history of smoking, medication known to interfere with neuromuscular blocking drugs, family or personal history of problems related to anaesthesia, acid reflux, or current upper airway infection were excluded. Vital signs monitoring consisted of arterial pressure recorded every 15 min, and heart rate, ECG, and arterial oxygen saturation were recorded continuously. Subjects were breathing room air throughout. An i.v. catheter was inserted into the antecubital vein in the left arm, and lactated Ringer's solution infused. Emergency equipment and drugs (including edrophonium for reversal of mivacurium block) were available at all times. If needed, study subjects were covered with blankets in order to maintain hand skin temperature >32°C.

**Recording of neuromuscular block and administration of mivacurium**

A Harvard infusion pump (Harvard Clinical Technology, Inc., Natick, MA, USA) was used to administer mivacurium i.v. In each study subject, we targeted a stable adductor pollicis (AP) TOF ratio within three different ranges: TOF ratio 0.85–0.95 (TOF ratio level 1), TOF ratio 0.65–0.75 (TOF ratio level 2), and TOF ratio 0.45–0.55 (TOF ratio level 3). The deepest level of block was determined based on previous reports showing that an AP TOF ratio of 0.4–0.5 is encountered not infrequently post-tracheal extubation during clinical anaesthesia.12 The initial infusion rate was 1.5 μg kg⁻¹ min⁻¹, a rate that was well tolerated by study subjects in a previous study.13 After a stable TOF ratio level was established, and measurements of clinical functions were made, we altered the mivacurium infusion rate by ±10–50% and waited for a new stable TOF ratio level to occur. After the final set of measurements, we terminated the infusion of mivacurium and the neuromuscular function was allowed to recover spontaneously. Because the mivacurium infusion rate needed to obtain a specific stable TOF ratio varies significantly between individuals, we did not randomize the order of block.14 Rather, we always started with a conservative infusion rate, targeting a shallower level of block, so as not to risk excessive initial paralysis in any volunteer.

Neuromuscular block was recorded at the left AP muscle at 15 s intervals using acceleromyography (AMG) (‘TOF Watch SX’, Merck & Co., Whitehouse Station, NJ, USA). A finger holder (Merck & Co.) applying ∼75 g preload to the thumb was used to enhance repeatability of the measurements.15

We did not use supra-maximal nerve stimulation because we believed that the volunteers would not tolerate that stimulus intensity for the duration of the study period. As reliable mean TOF ratio readings can be obtained as long as the stimulating current is maintained at >15 mA above the threshold for detection of the twitch response, supra-maximal stimulation is not required for AMG AP TOF measurements.16 17 Skin conductivity of electrical impulses may be greater in males than females under resting conditions, but the difference disappears during sympathetic stress.18 Therefore, the stimulus current was set 15 mA above threshold for the TOF Watch SX to detect thumb movement in both sexes. Every 15 min, the stimulus intensity was transiently increased by 5 mA to ensure that the stability of the TOF response was maintained.

The TOF ratio was monitored continuously, recorded electronically, and analysed later using TOFMON software (Merck & Co.). Four consecutive TOF ratios were averaged to obtain a single value. The mivacurium infusion was begun after obtaining a baseline TOF ratio value (difference in average TOF ratios recorded during the last and next last minute before start of the infusion <3%) after at least 10 min of continuous nerve stimulation at 15 mA above the threshold for response detection. During the mivacurium infusion, we considered that the TOF ratio had reached a stable level if values obtained 10 min apart differed <3%.

Uncorrected and normalized AMG AP TOF ratios were recorded at all levels of stable block. A normalized value was obtained by dividing each uncorrected TOF ratio with that subject’s baseline value. We recorded the time to establish each stable block level. The mivacurium infusion was terminated immediately if: the study subject asked to discontinue, signs of airway obstruction (stridor) occurred, complete loss of ability to swallow, or arterial oxygen saturation <90%.

**Clinical measures of muscle function**

We evaluated six clinical measures of muscle function. To ensure volunteer safety, the evaluations were performed every 5 min in order to detect rapid functional changes during non-steady-state plasma concentrations of mivacurium. Data for later analysis were obtained at stable TOF ratio levels.

**Ability to clench teeth**

We placed a wooden tongue depressor between the volunteer’s incisors and asked the volunteer to retain it while an investigator attempted to pull it out with his thumb and index fingers.13 Clenching was classified as either maintained or not maintained.
Ability to swallow

 Volunteers were asked to swallow saliva, and to subjectively grade if it felt normal or was more difficult than normal. Volunteers were continuously observed for signs of inability to swallow (e.g. drooling). If the volunteer reported maintained ability to swallow, then we conducted an additional swallowing test at stable blocks. The volunteer was asked to sip and swallow water using a straw or if the volunteer was unable to make a tight seal around the straw, 5 ml of water was placed behind the tongue using a syringe. Volunteers were considered unable to swallow if they reported that a saliva swallow could not be initiated or if they could not elevate the larynx. The water swallowing test was not performed if the ability to swallow was completely lost.

Ability to raise head > 5 s, ability to protrude the tongue, and ability to open the eyes were classified as either maintained or not maintained.

Handgrip strength

A calibrated dynamometer with a peak force indicator needle (Jamar 5030J1, Sammons Preston, Chicago, IL, USA) was used to measure the handgrip strength on the right side. Adequate repeatability and accuracy of the device has been demonstrated. During testing, the arm was resting on an arm board and an investigator stabilized the instrument. The volunteer was coached during the use of the device. The study subject was encouraged to squeeze the instrument with maximal strength, and then instructed to relax. Duplicate measurements were performed with an interval of 5 s of rest, and the mean of the two results was recorded.

Baseline evaluations of all functions were obtained before commencement of the mivacurium infusion, and recording continued until complete recovery from the effects of mivacurium. All assessments were performed in the supine position. The time needed to complete a series of tests was ~60 s. Each volunteer had therefore ~4 min of rest between test series. For safety reasons, the observer performing the tests was not blinded to the mivacurium infusion rate, but did not have access to the simultaneously obtained TOF ratio data. Also, the observer was unaware of results obtained by co-investigators.

Statistics

A power analysis was performed based on data obtained in a previous study where we observed a difference of 20% between males and females in handgrip strength, with inter-individual standard deviations of 7% (males) and 14% (females). Owing to the small numbers in that study (six males and six females), a 5% error margin in the estimate of the standard deviation was added [males 7 (5)%, females 14 (5)%. With these assumptions, the power analysis showed that 20 study subjects had to be enrolled to detect a 20% difference with >80% probability, assuming an α error <0.05.

We used the Wilcoxon signed-rank test to analyse the difference in the times needed to obtain the first and subsequent stable TOF ratio levels, and analysis of variance and the Newman–Keuls to test for differences between sexes in patient characteristics and in TOF ratios attained at each stable TOF ratio level. We analysed the sex-related difference in the relationships between AMG AP TOF ratio and continuous variables (i.e. mivacurium infusion rate and handgrip strength) using a multivariate linear model for TOF ratio, sex, and their interaction. The outcome measure was developed, fully accounting for repeated measures. The lower–upper 95% confidence intervals (CIs) of the slopes were calculated and compared between sexes, inferring a significant difference if there was no overlap. The statistical analyses were made using JMP version 7.0 (SAS Institute, Cary, NC, USA). We tested the relationships between AMG AP TOF ratio and ordinal functions (i.e. ability to clench teeth, raise head > 5 s, and swallow) by logistic regression analysis, performed using NONMEM (version VI). The Laplacian method of estimation was used to correctly account for repeated measures within individuals. We tested the difference between males and females using a likelihood ratio test.

In all statistical analyses, normalized TOF ratio values were used. The significance level was set at P<0.05.

Results

Body weight was significantly greater in males than females (P<0.001), but age and BMI were similar. All subjects completed the study. Oxygen saturation was never <95% in any individual. No evidence of aspiration during swallowing tests was detected. The hand skin temperature over the thenar region on the recording side was maintained >32°C at all times.

The TOF ratio rapidly recovered to baseline value after termination of the mivacurium infusion in all volunteers. The times needed to establish the three successive stable TOF ratio levels were similar between sexes (74 (21) and 71 (12), 30 (5) and 39 (7), and 34 (9) and 28 (4) min, in males and females, respectively). The time needed to establish the first attained stable TOF ratio level was significantly longer than for either the second or third TOF ratio level in both sexes (P<0.001). The TOF ratio at level 3 was significantly lower in females than males (P<0.05, Table 1).

In 13 subjects, the first attained stable TOF ratio was at level 1 (6M/7F), in five at level 2 (3M/2F), and in two at level 3 (1M/1F).

Mivacurium infusion rates and resultant TOF ratios are shown in Table 1, and the results of univariate and multivariate analysis on the relationship between mivacurium infusion rate and normalized TOF ratio in Table 2. The lower–upper CI range of the slopes slightly overlaps between sexes. However, the interaction term was significant (P=0.016), suggesting that a sex-related difference in this relationship exists.

For the clinical measures of muscle function, the ability to protrude the tongue and open the eyes was well preserved at all TOF ratio levels in all subjects. The proportion of individuals losing the ability to clench teeth and raise head > 5 s increased with a reduction in TOF ratio in both sexes.
Table 1 Stable neuromuscular blocks (TOF ratio uncorrected and normalized to baseline value) obtained during steady-state continuous infusions with mivacurium (µg kg⁻¹ min⁻¹). All data are mean (sd) (range). M, males; F, females. *Significantly higher in males than females at TOF ratio level 3

<table>
<thead>
<tr>
<th>Variable/group</th>
<th>Baseline M</th>
<th>TOF ratio level 1 M</th>
<th>TOF ratio level 2 M</th>
<th>TOF ratio level 3 M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mivacurium infusion rate (µg kg⁻¹ min⁻¹)</td>
<td>0.0</td>
<td>1.48</td>
<td>1.86</td>
<td>2.36</td>
</tr>
<tr>
<td>Range</td>
<td>0.8–2.4</td>
<td>1.0–2.7</td>
<td>1.4–3.3</td>
<td>1.4–3.0</td>
</tr>
<tr>
<td>TOF ratio (%) normalized</td>
<td>115</td>
<td>96</td>
<td>76</td>
<td>57*</td>
</tr>
<tr>
<td>Range</td>
<td>94–140</td>
<td>75–135</td>
<td>52–105</td>
<td>26–95</td>
</tr>
</tbody>
</table>

Table 2 Univariate and multivariate analyses of the relationships between normalized TOF ratio (TOF) and mivacurium infusion rate (MIR) and between percentage reduction in normalized TOF ratio (%TOF) and percentage reduction in handgrip strength (%HGS). CI, confidence interval

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Variable/group</th>
<th>Slope</th>
<th>SD</th>
<th>P-value</th>
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<th>Upper 95% CI</th>
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</thead>
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<tr>
<td>Univariate</td>
<td>TOF vs MIR</td>
<td>Females</td>
<td>25.42</td>
<td>8.75</td>
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<td>19.75</td>
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<td></td>
<td>Males</td>
<td>18.49</td>
<td>5.54</td>
<td>&lt;0.0001</td>
<td>14.92</td>
<td>22.07</td>
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<tr>
<td></td>
<td>All</td>
<td>21.28</td>
<td>7.38</td>
<td>&lt;0.0001</td>
<td>18.01</td>
<td>24.55</td>
</tr>
<tr>
<td>Univariate</td>
<td>%TOF vs %HGS</td>
<td>Females</td>
<td>0.0101</td>
<td>0.002</td>
<td>&lt;0.0001</td>
<td>0.0086</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>0.0146</td>
<td>0.003</td>
<td>&lt;0.0001</td>
<td>0.0127</td>
<td>0.0165</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>0.0118</td>
<td>0.002</td>
<td>&lt;0.0001</td>
<td>0.0105</td>
<td>0.0131</td>
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<tr>
<td>Multivariate</td>
<td>TOF vs MIR</td>
<td>Gender</td>
<td>4.1600</td>
<td>6.20</td>
<td>0.050</td>
<td>−0.0006</td>
</tr>
<tr>
<td></td>
<td>MIR</td>
<td>21.9663</td>
<td>5.02</td>
<td>&lt;0.0001</td>
<td>18.7856</td>
<td>25.1470</td>
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<tr>
<td></td>
<td>Interaction term</td>
<td>3.9400</td>
<td>5.02</td>
<td>0.016</td>
<td>0.7593</td>
<td>7.1207</td>
</tr>
<tr>
<td>Multivariate</td>
<td>%TOF vs %HGS</td>
<td>Gender</td>
<td>−0.0667</td>
<td>0.077</td>
<td>0.017</td>
<td>−0.1162</td>
</tr>
<tr>
<td></td>
<td>%HGS</td>
<td>0.0123</td>
<td>0.002</td>
<td>&lt;0.0001</td>
<td>0.0112</td>
<td>0.0135</td>
</tr>
<tr>
<td></td>
<td>Interaction term</td>
<td>−0.0022</td>
<td>0.002</td>
<td>0.0004</td>
<td>−0.0034</td>
<td>−0.0010</td>
</tr>
</tbody>
</table>

Males lost the ability to clench teeth and raise head >5 s at significantly higher TOF ratios than females (P<0.001 and 0.01, respectively). The relationships between normalized TOF ratio and the probability of losing the ability to clench teeth and raise head >5 s are shown in Figures 1 and 2. Swallowing became subjectively more difficult with decreasing TOF ratio in all study subjects and the function was lost in eight males and two females at TOF ratio level 3 (Table 3). However, the difference between sexes regarding ability to swallow did not reach the significance level (P=0.05).

The ability to clench teeth was lost in four males, but in none of the females, at an uncorrected (non-normalized) TOF ratio >0.9, and in six males and only one female at an uncorrected TOF ratio >0.8 (data not shown). All three functions (teeth clenching, head raise >5 s, swallowing) were maintained in all study subjects at normalized TOF ratio >0.9.

The difference between duplicate measurements of handgrip strength was consistently <5%. The handgrip strength decreased significantly with decreasing TOF ratio in all volunteers (Tables 2 and 3). The percentage decrease in handgrip strength from baseline was significantly greater in males than females at all TOF ratio levels (Table 2). The mean absolute handgrip strength at baseline was 62% greater in males than females. At TOF ratio level 3, the mean absolute handgrip strength was similar in males and females, despite the males having a significantly greater TOF ratio (Tables 1 and 3).

**Discussion**

We studied the relationship between AMG AP TOF ratio and measures of neuromuscular function that are readily available for evaluation in a clinical setting, measures frequently...
Table 3 Clinical measures obtained at baseline and three different levels of stable mivacurium block in 20 volunteers. S/L, maintained or lost function. M, males; F, females. *Significantly different; males vs females

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>TOF ratio level 1</th>
<th>TOF ratio level 2</th>
<th>TOF ratio level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Mean handgrip strength (kg)</td>
<td>47*</td>
<td>29</td>
<td>29*</td>
<td>21</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>34–70</td>
<td>14–40</td>
<td>20–37</td>
<td>10–30</td>
</tr>
<tr>
<td>Percentage reduction in handgrip strength</td>
<td>0</td>
<td>0</td>
<td>35*</td>
<td>26</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Range</td>
<td>0</td>
<td>0</td>
<td>16–66</td>
<td>5–52</td>
</tr>
<tr>
<td>Ability to clench teeth</td>
<td>10S/0L</td>
<td>10S/0L</td>
<td>8S/2L</td>
<td>10S/0L</td>
</tr>
<tr>
<td>Ability to swallow</td>
<td>10S/0L</td>
<td>10S/0L</td>
<td>10S/0L</td>
<td>10S/0L</td>
</tr>
<tr>
<td>Ability to raise head &gt;5 s</td>
<td>10S/0L</td>
<td>10S/0L</td>
<td>10S/0L</td>
<td>10S/0L</td>
</tr>
</tbody>
</table>

Fig 1 Results of a logistic regression analysis of the relationship between the probability of loss of ability to clench teeth and AMG AP TOF ratio in males and females. NONMEM (version VI) was used in the analysis and the Laplacian method of estimation was used to account for repeated measures within each individual. Each individual contributes four data points (baseline and three different levels of stable neuromuscular block). The relationships are significantly different between males and females (P<0.001).

Fig 2 Results of a logistic regression analysis of the relationship between the probability of loss of ability to raise the head > 5 s and AMG AP TOF ratio in males and females. NONMEM (version VI) was used in the analysis and the Laplacian method of estimation was used to account for repeated measures within each individual. Each individual contributes four data points (baseline and three different levels of stable neuromuscular block) (P<0.01).
used to assess the recovery from neuromuscular block. We demonstrated significant sex-related differences in three of these relationships: the ability to clench teeth and raise head >5 s, and in the percentage change in handgrip strength. In fact, the baseline difference between sexes in absolute handgrip strength (62%) completely disappeared at TOF ratio level 3, despite significantly greater TOF ratio in males (Table 3). The difference regarding the ability to swallow did not quite reach the statistical significance level (P=0.05), but that may have been achieved if more subjects had been included. The sex-related difference in the ability to clench teeth may have important clinical implications because this muscle function is involved in the maintenance of upper airway patency. The function of the genioglossus muscle, the most important upper airway-patency muscle, appeared to be unchanged in all our study subjects when tested in a very crude way (tongue protrusion). However, functional changes of this muscle have been observed at an uncorrected TOF ratio 0.9 when studied using an EMG technique. Therefore, maintained ability to protrude the tongue does not preclude sex-related differences in the function of the genioglossus muscle during partial neuromuscular block.

Our results suggest that males may be more vulnerable to the residual effects of neuromuscular blocking drugs in the postoperative period than females. However, a greater neuromuscular blocking drug-related complication rate in males than females has not been reported. There is no obvious reason why the relationships between AP TOF ratio and certain muscle functions are different between sexes. It has been shown that handgrip fatigue develops earlier in males than females upon repeated maximal contractions (48 contractions at 5 s intervals). However, in our experiment, only two contractions with 5 s intervals were performed, and the difference in magnitude between duplicate measurements was always <5%. Therefore, fatigue development is not a likely explanation of the observed sex-related difference in the TOF ratio vs handgrip strength relationship. We were meticulous when establishing stable TOF ratios, and therefore pharmacokinetics should not be a confounding factor. However, the results in the present study do not preclude pharmacodynamic reasons.

We chose to record both uncorrected and normalized TOF ratios, for two reasons. First, baseline AMG AP TOF ratios deviate from 100% in most individuals. In our study, 19 of 20 subjects had TOF ratio >100%, and the variability was large (94–140%). This is in agreement with previous studies. It is therefore necessary to normalize the TOF ratio values to obtain meaningful data, that is, data that can be compared between individuals. We trust this technique because we observed that in all study subjects, the TOF ratio recovered to its baseline value, even after 3 h of mivacurium block. Secondly, in the present investigation, 40% of the males, but none of the females, were unable to clench the teeth at an uncorrected TOF ratio >0.9, the recommended endpoint for reversal of neuromuscular block during clinical anaesthesia. The results from our study therefore clearly show that in a clinical setting, the observation of an uncorrected AMG TOF ratio of 0.9 does not guarantee adequate recovery from neuromuscular block, at least not in male subjects. Only a normalized AMG AP TOF ratio >0.9 was associated with normal muscle functions in all volunteers. When recording the neuromuscular function objectively during anaesthesia, we therefore recommend that the anaesthetist takes into account the baseline value of the TOF ratio. We suggest that normalization of the TOF ratio is added as an optional function in future models of the TOF Watch monitor.

The relationship between the mivacurium infusion rates and stable TOF ratios was different between males and females. A significantly greater infusion rate was needed in males at all stable TOF ratio levels, even at TOF ratio level 3 where the mean TOF ratio was greater in males than females. This finding may be caused by physiological differences between sexes. First, the level of cholinesterase activity is greater in males than females. Secondly, the distribution volume of mivacurium must be expected to be greater in males than females due to sex-related differences in the relationship between body weight and body content of water. However, measurements of plasma concentrations of mivacurium are needed to determine if the relationship between AP TOF ratio and the blood concentration of mivacurium is similar between sexes.

The times needed to establish stable TOF ratio levels were significantly longer for the first compared with subsequent blocks, as described in our previous study. This delayed onset of effect may be related to the fact that >70% of the post-junctional acetylcholine receptors must be blocked before any change in neuromuscular function is observed. Our study design, using low-dose constant-rate infusions of a neuromuscular blocking drug, created favourable conditions for this. We could also speculate that the least active isomer of mivacurium (cis–cis), with a long elimination half-life (53 min) and a large distribution volume (0.35 litre kg⁻¹), may induce small changes in the TOF ratios after longer infusions. However, the times needed to establish stable TOF ratios did not differ between sexes.

In this investigation, four different comparisons between sexes were made (i.e. in the relationships between TOF ratio and ability to clench teeth, swallow, raise head >5 s, and percentage reduction in handgrip strength). Often, when multiple testing is performed, some kind of correction is needed to eliminate erroneous statistically significant differences. However, in this study, all the tests of muscle function were interrelated (all functions based on muscle activity, all muscle groups exposed to the same mivacurium plasma concentration, and all functions related to the same AMG AP TOF ratio). It is therefore to be expected that the relationships (AMG AP TOF ratio vs any of the muscle functions) should follow the same direction. Under such conditions, compensation for multiple measurements is not indicated.
In conclusion, we have found that residual neuromuscular block, as measured by AMG TOF ratio, manifests differently in men and women. The ability to clench the teeth and raise the head >5 s fails at greater TOF ratios in males than females, and the percentage reduction in handgrip strength from baseline is greater in males than females at any TOF ratio level. We found that a non-normalized TOF ratio of 0.9 does not guarantee adequate reversal of neuromuscular block. In contrast, a normalized (to the baseline value) TOF ratio of 0.9 was always associated with recovery of clinical functions. Therefore, we recommend that a normalized TOF ratio of 0.9 is targeted as the endpoint for adequate reversal of neuromuscular block.

Declaration of interest
None declared.

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