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Manual Evaluation of Residual Curarization Using Double Burst Stimulation: A Comparison with Train-of-four

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Double burst stimulation (DBS) is a new mode of stimulation developed to reveal residual neuromuscular blockade under clinical conditions. The stimulus consists of two short bursts of 50 Hz tetanic stimulation, separated by 750 ms, and the response to the stimulation is two short muscle contractions. Fade in the response results from neuromuscular blockade as with train-of-four stimulation (TOF). The authors compared the sensitivity of DBS and TOF in the detection of residual neuromuscular blockade during clinical anaesthesia. Fifty-two healthy patients undergoing surgery were studied. For both stimulation patterns the frequencies of manually detectable fade in the response to stimulation were determined and compared at various electromechanically measured TOF ratios. A total of 369 fade evaluations for DBS and TOF were performed. Fade frequencies were statistically significantly higher with DBS than with TOF, regardless of the TOF ratio level. Absence of fade with TOF implied a 48% chance of considerable residual relaxation as compared with 9% when fade was absent with DBS. The results demonstrate that DBS is more sensitive than TOF in the manual detection of residual neuromuscular blockade. (Key words: Monitoring: double burst stimulation; train-of-four. Neuromuscular transmission: nerve; stimulation.)

OVER THE PAST two decades, train-of-four (TOF) stimulation has been established as the pattern of stimulation for clinical monitoring of neuromuscular blockade.[1] This stimulation mode allows for convenient and reliable tactile evaluation of moderate degrees of nondepolarizing blockade,[2] and is of special value in the adjustment of individual dose regimens for neuromuscular blocking drugs during anesthesia. However, during recovery it is difficult manually or visually to estimate the TOF ratio with sufficient certainty to exclude residual curarization.[3,4]

Double burst stimulation (DBS) is a new pattern of stimulation that was developed to reveal residual neuromuscular blockade. DBS consists of two short tetanic bursts separated by 750 ms. Our previous study indicated that a DBS with three impulses in each of two tetanic bursts of 50 Hz ($DBS_{3,3}$) is most suitable for clinical use.[5] The duration of each square-wave impulse in the bursts is 200 μs (fig. 1). In the nonparalyzed muscle, the response to $DBS_{3,3}$ is two short muscle contractions of equal strength. In the partly paralyzed muscle, the second response is weaker than the first, *i.e.*, there is fade in the response (fig. 2).

In our preliminary study of the applicability of DBS in manual detection of residual neuromuscular blockade,[5] no direct comparison was performed between TOF and DBS responses evaluated manually. Also, the response to DBS was evaluated at one arm while the TOF ratio was measured at the other arm. Therefore, this controlled study was undertaken to investigate whether $DBS_{3,3}$ is more sensitive than the TOF method in the manual detection of residual blockade during clinical anesthesia.

Materials and Methods

The study was approved by the authors' institution's ethics committee. The patients entered the study without giving informed consent because perioperative neuromuscular monitoring is used routinely at our department. Fifty-two patients, ASA Class I or II, undergoing elective lower abdominal procedures or mastectomies entered the study. None of the patients had neuromuscular diseases or received any medication that might alter neuromuscular transmission.

One hour after premedication with diazepam 0.2 mg/kg orally, anesthesia was induced with thiopental 3–5 mg/kg and fentanyl 0.1 mg iv. Anesthesia was maintained with nitrous oxide 66.6% in oxygen, and either halothane 0.8–1.5% delivered concentration, as indicated by a Fluotec Mark III® vaporizer, or dehydrobenzperidol 5–10 mg and fentanyl 0.005 mg/kg iv. Increments of 0.05–0.1 mg of fentanyl were administered iv when necessary.

After induction of anesthesia, the ulnar nerve was stimulated by a Myotest® DBS nerve stimulator (Biometer, Denmark) *via* cutaneous electrodes placed at the wrist, using supramaximal stimuli. The resultant adduction force of the corresponding thumb was measured and recorded by means of a force transducer connected to the Myograph® equipment (Biometer, Denmark).[6] A preload of 300 g was used throughout. When the response to 1 Hz single twitch stimulation had stabilized for 6–8 min, atracurium 0.05 mg/kg, followed 4 min later by succinylcholine 1.5 mg/kg, was administered iv to facilitate endotracheal intubation. After the response to 1 Hz single

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twitch, stimulation had returned to control values, the pattern of stimulation was changed to TOF, and further relaxation was given as either repeated small bolus doses or a continuous infusion of atracurium.

Continuous surveillance of the degree of neuromuscular blockade, as specified by the TOF ratio, was done by one member of the group. This person also made minor alterations in the depth of blockade but performed no clinical evaluations. The measured TOF ratios were unknown to the investigators.

At different TOF ratios the thumb was loosened from the force transducer and one investigator evaluated the response to TOF and thereafter $DBS_{3,3}$. The evaluations were quantified as either "fade" or "no-fade," and the results of the evaluation had to be available within a few seconds. An intermission of 10 s between TOF and DBS was chosen to avoid facilitation of the DBS response. After evaluation the thumb was replaced in the force transducer and TOF ratio was measured again. To avoid facilitation of the mechanical TOF response after the manual evaluation of both TOF and DBS, the control TOF measurements were performed at least 20 s after the DBS stimulation.[5]

The clinical evaluations were excluded from the study in case the TOF ratio was altered by more than 0.05, relative to the value immediately before manual evaluation. Evaluations were also excluded if the two values were not both within one of the following TOF ratio intervals: 1) ≤0.4; 2) 0.41–0.50; 3) 0.51–0.60; 4) 0.61–0.70; and 5) >0.7.

After termination of surgery, neuromuscular blockade was antagonized with atropine/neostigmine so that measured TOF ratio was above 0.8 before tracheal extubation was performed.

On the basis of their experience in neuromuscular monitoring, the investigators were divided into two groups: group 1 comprised two persons with more than 5 yr of experience in neuromuscular monitoring and group 2 consisted of three persons with 1–1.5 yr of experience.

The frequencies of clinically detectable fade in the response to each stimulation pattern were compared within each TOF ratio interval for each group of investigators. The results for the two groups of investigators were also compared.

In some patients, clinical evaluations were performed by the same observer at each TOF ratio interval. Although these evaluations were not performed with any specified sequence in relation to the TOF ratio, a threshold for fade could be established for both patterns of stimulation. The threshold was defined as the highest TOF ratio interval where fade was present. The distribution of the established thresholds were compared for the two patterns of stimulation.

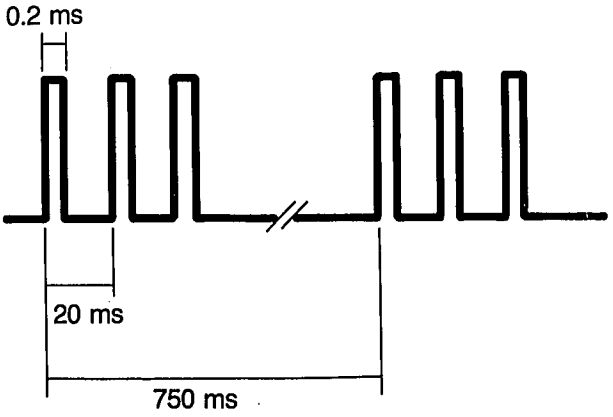

FIG. 1. Stimulation pattern of DBS.

The McNemar and chi-square tests were applied for comparison of frequencies, and the level of significance was set at $P < 0.05$.

Inverse probabilities were calculated using Bayes' formula[7] with prevalence rates 0.2 for each TOF ratio interval (*i.e.*, every interval was *a priori* considered equally likely).

Results

Figure 3 shows, for each TOF ratio interval, the number of clinical evaluations performed and the number of evaluations with and without manually recognizable fade. Because there was no statistically significant difference between the results in groups 1 and 2, the data for the two groups were pooled. A total of 369 evaluations were performed. A statistically significantly higher frequency was found for fade with $DBS_{3,3}$, as compared with TOF, regardless of the TOF ratio interval. Invariably, when fade could be felt in the TOF response, fade in the DBS response was also present. There were no false-positive evaluations, *i.e.*, in no case was fade felt when it actually was not present in the mechanical response.

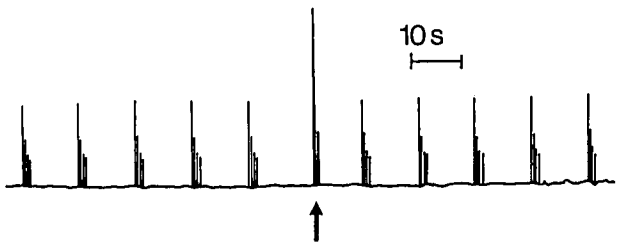

FIG. 2. Mechanical twitch recording of the TOF and the $DBS_{3,3}$ response. (*Arrow*) Response to DBS. Note the fade in response to both modes of stimulation.

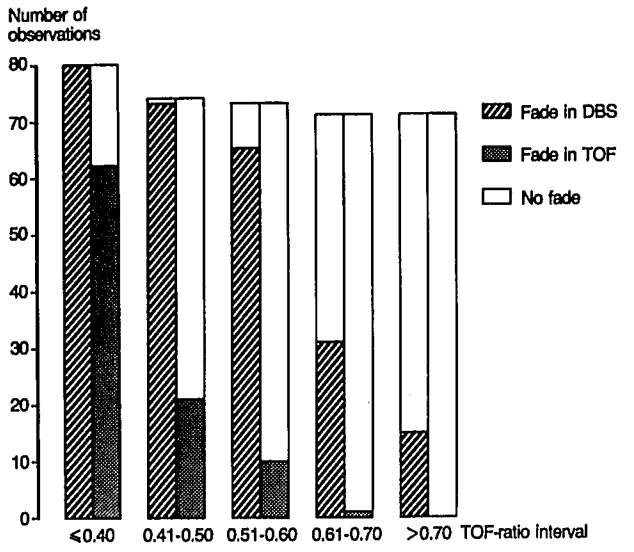

FIG. 3. Manually detectable fade in response to DBS and TOF. (*Left column*) DBS. (*Right column*) TOF.

A total of 37 thresholds for fade were established. Figure 4 shows the distribution of thresholds among the TOF ratio intervals. Regardless of the investigators' experience, the threshold for fade with DBS was statistically significantly higher than that for TOF.

Table 1 displays the inverse probabilities (*i.e.*, the probability of being within a certain TOF ratio interval, when clinical fade evaluations for TOF and DBS are given). As shown, absence of fade in the response to TOF stimulation implies a 52% chance (0.26 + 0.26) that measured TOF ratio will be above 0.6. An observation of absence of fade

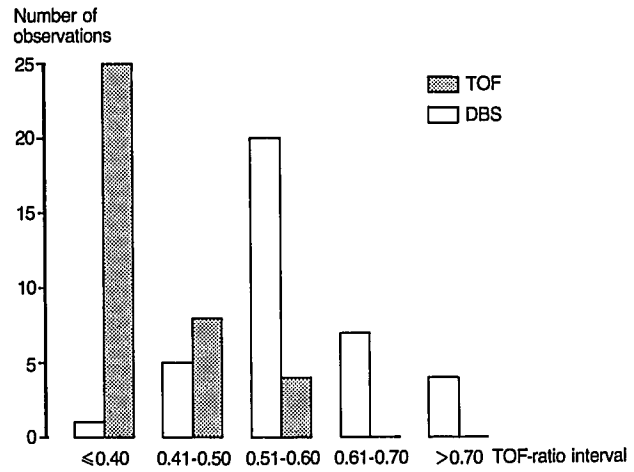

FIG. 4. Threshold for fade with DBS and TOF. Distribution of 37 established thresholds for fade in DBS and TOF among defined TOF ratio intervals.

TABLE 1. Probability of Being within Defined TOF Ratio Intervals When Different Clinical Fade Evaluations Are Given

TOF Ratio	Clinical Evaluation		
	No Fade in TOF Regardless of DBS	No Fade in Either TOF or DBS	No Fade in TOF but Fade in DBS
≤0.40	0.06	0.00	0.10
0.41–0.50	0.19	0.01	0.30
0.51–0.60	0.23	0.07	0.33
0.61–0.70	0.26	0.38	0.18
>0.70	0.26	0.53	0.09

in the response to $DBS_{3,3}$ results in an improvement in this number to 91% (0.38 + 0.53). Conversely, if there is no fade in the response to TOF but fade with $DBS_{3,3}$, the figure decreases to 27% (0.18 + 0.09).

Discussion

The results of this study clearly indicate that $DBS_{3,3}$ is more sensitive than the TOF method in normal detection of residual neuromuscular blockade. However, our results also indicate that the problems connected with manual detection of postoperative residual neuromuscular blockade have not been completely solved with the introduction of the present DBS mode ($DBS_{3,3}$).

In accordance with previous findings,[2] we have found that only TOF ratios below 0.40 can be diagnosed using manual evaluation of the TOF response (figs. 3 and 4). In contrast, manual evaluation of the $DBS_{3,3}$ response allows for detection of a TOF ratio below 0.60. However, it is generally agreed upon that to ensure adequate clinical recovery the TOF ratio has to be ≥0.70.[8,9] This level of recovery cannot be diagnosed using either TOF or $DBS_{3,3}$ stimulation (table 1; fig. 3). The probability analysis shows that when there is no manually detectable fade in either the TOF or the $DBS_{3,3}$ response, there is still a 47% risk (1–0.53; table 1) that the true TOF ratio is below 0.70, and this number is not improved with increasing experience in manual evaluation of the response to nerve stimulation. In this respect, our results are in accordance with previous findings.[3]

As indicated earlier, the investigators did not know the level of neuromuscular blockade at the time of the manual evaluation. The study was performed in patients undergoing operations in which deep neuromuscular blockade was not essential, and the investigators did not know for sure whether or not a neuromuscular blocking drug had been given. When a muscle relaxant was used, minor changes in the level of neuromuscular blockade were often induced to exclude that investigators, performing several consecutive evaluations, would have the idea that the block inevitably decreased with time. The response to

TOF and DBS are different and instantaneously recognizable, rendering a blind comparison impossible. The investigator always knew whether he was evaluating TOF or DBS, and his decision as to whether fade was present in the last of two evaluations might be influenced by the first of these two evaluations. To minimize this bias, TOF, as the presumed least sensitive mode of stimulation, was always evaluated before DBS. Also, to minimize bias, the results of the manual evaluation had to be given immediately and independently for each pattern of stimulation. In this way, absence of fade with TOF induced a minimal prejudice as to whether fade should be present with the following DBS or not. Conversely, the presence of fade in TOF response might have induced bias. From a clinical viewpoint, however, fade in the response to TOF means inadequate recovery from neuromuscular blockade, rendering further evaluation by means of DBS superfluous. In clinical practice evaluation of DBS is normally relevant only when there is no fade in the TOF response.

In conclusion, during recovery and in the postoperative period, manual evaluation of the response to $DBS_{3,3}$ is superior to manual evaluation of the response to TOF stimulation. Absence of fade in response to $DBS_{3,3}$ normally excludes severe residual neuromuscular blockade (TOF < 0.60) but does not necessarily indicate adequate clinical recovery. The possibility exists that the diagnostic sensitivity and specificity of the DBS can be improved by changing one or more of the variables in the DBS.[5]

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