Double burst stimulation$_{2,3}$: a new stimulating pattern for residual neuromuscular block

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Purpose: *We present a new stimulating pattern: double burst stimulation$_{2,3}$ (DBS$_{2,3}$) for evaluating residual neuromuscular block.*

Methods: *Forty adult patients were studied. For DBS$_{2,3}$, two burst stimuli were applied every 750 msec. The first consisted of two tetanic stimuli of 0.2 msec duration and the second of three tetanic stimuli of 0.2 msec duration. At varying degrees of neuromuscular block induced by vecuronium, the presence or absence of fade, or the presence or absence of waxing (i.e., the feeling that the muscular contraction in response to the second burst was stronger than that to the first) was determined by an observer blinded to the depth of neuromuscular block. In addition, the relationship between the train-of-four (TOF) ratio and DBS$_{2,3}$ ratio was established at varying depths of neuromuscular block (TOF ratio 0.04–1.00).*

Results: *The probabilities of tactile detection of fade in response to DBS$_{2,3}$ were 100, 76, 15, 9, 3, 0, and 0% at a TOF ratio of 0–0.40, 0.41–0.50, 0.51–0.60, 0.61–0.70, 0.71–0.80, 0.81–0.90, and 0.91–1.00, respectively. Waxing in response to the DBS$_{2,3}$ was identified in 0, 6, 32, 84, and 98% of cases when the TOF ratios were 0.00–0.60, 0.61–0.70, 0.71–0.80, 0.81–0.90, and 0.91–1.00, respectively. A close linear relationship existed between the TOF ratio and DBS$_{2,3}$ ratio (r = 0.96, $P < 0.000001$).*

Conclusion: *DBS$_{2,3}$ is of clinical use because when residual neuromuscular block is clinically important, fade can be identified, but once neuromuscular function returns to a sufficient level, waxing can be detected.*

Objectif: *Les auteurs présentent un nouveau mode de stimulation, le double burst 2,3 (DBS$_{2,3}$) pour évaluer la curarisation résiduelle.*

Méthodes: *L'étude portait sur 40 adultes. Pour le DBS$_{2,3}$, deux stimuli ont été appliqués aux 750 msec. Le premier était formé de deux stimuli tétaniques de 0,2 msec et le second de trois stimuli tétaniques de 0,2 msec. A différents niveaux de curarisation au vécuronium, la présence ou l'absence de fade (fatigue) et l'absence de waxing (impression que la concentration musculaire en réponse à la deuxième stimulation était plus importante que la première) étaient évaluées par un observateur ignorant la profondeur du bloc neuromusculaire. En outre, la relation entre le ratio du train-de-quatre (TOF) et le ratio du DBS$_{2,3}$ a été établie à différents niveau de curarisation.*

Résultats: *Les probabilités de détection du fade en réponse au DBS$_{2,3}$ étaient de 100, 76, 15, 9, 3 et 0% à des ratios de TOF respectifs de 0,00–0,40, 0,41–0,50, 0,51–0,60, 0,61–0,70, 0,71–0,80, 0,81–0,90, et 0,91–1,00. Le waxing en réponse au DBS$_{2,3}$ étaient identifié dans 0, 6, 32, 84, et 98% des cas à des ratios respectifs de TOF de 0,00–0,60, 0,61–0,70, 0,71–0,80, 0,81–0,90, et 0,91–1,00. Il existait une relation linéaire étroite entre le ratio du TOF et le ratio du DBS$_{2,3}$ (r = 0,96, $P <$ 0,000001).*

Conclusion: *Le DBS$_{2,3}$ est utile en clinique parce qu'on peut identifier le fade quand la curarisation résiduelle est importante cliniquement; lorsque la fonction neuromusculaire revient à un niveau adéquat, on peut aussi détecter le waxing.*

Key words

MONITORING: neuromuscular junction, double burst stimulation;
NEUROMUSCULAR RELAXANTS: vecuronium.

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To assess residual neuromuscular block, double burst stimulation$_{3,3}$ (DBS$_{3,3}$) or DBS$_{3,2}$ is commonly applied clinically.[1,2] It has been reported that a train-of-four (TOF) ratio of 0.74 correlates well with signs of adequate clinical recovery of neuromuscular transmission.[3]

However, at a TOF ratio of 0.71–0.80, fade in response to $DBS_{3,3}$ stimulation can be identified by touch in only 24% of patients.[1] Thus, using $DBS_{3,3}$ adequate recovery from neuromuscular block cannot be diagnosed. In contrast, even when the TOF ratio returns to 0.81–0.90 and 0.91–1.00, fade in response to $DBS_{3,2}$ is felt manually in as many as 63% and 33% of patients, respectively.[1] Thus, with $DBS_{3,2}$, anaesthetists may have a false impression that the depth of the residual neuromuscular block is important.

On the other hand, to assess the degree of the recovery from neuromuscular block, the presence or absence of fade in response to nerve stimulation has traditionally been examined. We hypothesized that if the number of tetanic stimuli in the first burst in DBS was less than that in the second, fade would be felt when recovery from neuromuscular block was inadequate, and the fade would become impalpable as the block subsided. Finally, muscular contraction in response to the second burst of $DBS_{2,3}$ would feel stronger than that to the first when the level of recovery was satisfactory.

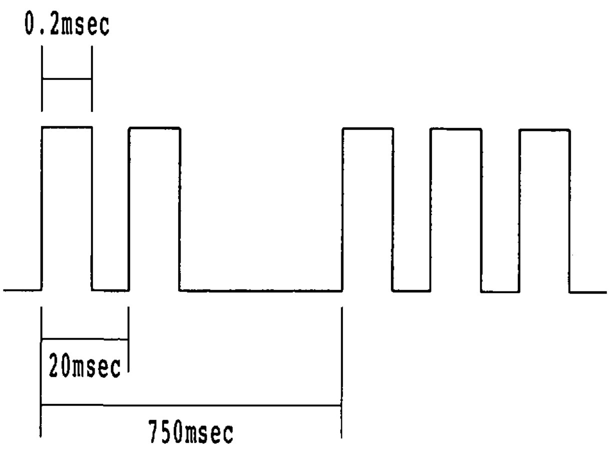

FIGURE 1 Stimulating pattern for double burst stimulation$_{2,3}$ ($DBS_{2,3}$). The $DBS_{2,3}$ consists of two burst stimuli separated by 750 msec. The first burst consists of two 50 Hz tetanic stimuli of 0.2 msec duration, and the second of three 50 Hz tetanic stimuli of 0.2 msec duration.

Methods

Written informed consent was obtained from each subject and the protocol was approved by our institutional ethical committee. Forty adult patients, ASA physical status 1–2, scheduled for elective surgical procedures in which intense neuromuscular block was not essential were enrolled in the study. No patient had neuromuscular, hepatic, or renal disease, or was taking any drug known to affect the action of neuromuscular relaxants.

Premedication, consisting of atropine 0.01 $mg \cdot kg^{-1}$ and hydroxyzine 1.0 $mg \cdot kg^{-1}$ *im*, was administered 30 min before induction of anaesthesia. On both forearms, surface stimulating electrodes (Vitrodes, M-150, Nihon-Kohden Inc., Tokyo, Japan) were positioned over the ulnar nerve at the wrist. One hand and forearm (control arm) was immobilized and a force transducer was attached to the thumb. The other hand and forearm (test arm) was unrestrained. After administration of 5.0 $mg \cdot kg^{-1}$ thiopentone *iv*, train-of-four (TOF) stimuli were delivered at 50 mA every 20 sec to both forearms using an electrical stimulator (Isolator, SS-102 J, Nihon-Kohden Inc., Tokyo, Japan). For TOF stimulation, four trains of single twitch stimuli consisting of 0.2 msec square-waves were given at a frequency of two Hz. The corresponding mechanical twitch responses of adduction of the thumb of the fixed arm were measured using a force transducer and were recorded on a paper chart of a neuromuscular transmission analyzer (Myograph 2000, Biometer International, Odense, Denmark). The mechanical twitch height in response to T_1 (the first stimulation in TOF) was regarded as the control twitch height. After obtaining the control twitch height 0.1 $mg \cdot kg^{-1}$ vecuronium *iv* was administered and tracheal intubation performed. Anaesthesia was maintained with nitrous oxide 66% in oxygen and isoflurane (1.0% end-tidal concentration). The patients' lungs were ventilated to maintain normocapnia ($P_{ET}CO_2$ 32–37 mmHg). The concentrations of anaesthetics and $P_{ET}CO_2$ were measured using a multiple gas monitor (Capnomac Ultima, S-31-03, Datex Inc., Helsinki, Finland). The peripheral skin temperature over the adductor pollicis muscle of the investigated arm was monitored using a surface skin thermometer (Terumo-Finer, CTM-303, Terumo Inc., Tokyo, Japan).

Thereafter, a continuous infusion of vecuronium at a rate of 70–160 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ was established to achieve a stable degree of neuromuscular block (TOF ratio of 0.04–1.00). Once the TOF ratio varied by less than 10% for five minutes, $DBS_{2,3}$ was applied to both forearms. Twenty seconds elapsed between the TOF and $DBS_{2,3}$, and 20 sec after $DBS_{2,3}$, the TOF stimuli were again delivered every 20 sec. As shown in Figure 1, $DBS_{2,3}$ consisted of two burst stimuli separated by 750 msec. The first burst consisted of two 50 Hz tetanic stimuli of 0.2 msec duration, and the second of three 50 Hz tetanic stimuli of 0.2 msec duration. A personal desk-top computer (PC-9801 UX, NEC Inc., Tokyo, Japan) was used for overall control of the automatic stimulation.

When DBS was applied to the test arm, the presence or absence of fade, or the presence or absence of waxing i.e., a feeling that the muscular contraction in response to the second burst was stronger than that to the first was determined by an observer blinded to the true depth of neuromuscular block, whilst simultaneous recordings of the responses in the contralateral arm (control arm) were made. Twelve blinded observers, all anaesthesia residents, took part in the tactile assessment of fade or waxing. Each observer participated in the determination of presence of fade or waxing in the same patient only once.

Correlation of the TOF ratio to the $DBS_{2,3}$ ratio was investigated at varying depths of neuromuscular block (TOF ratio 0.04–1.00). The TOF ratio measured just before the $DBS_{2,3}$ was regarded as the TOF ratio corresponding to the three types of DBS.

At the end of the surgical procedure, 0.02 $mg \cdot kg^{-1}$ atropine and 0.04 $mg \cdot kg^{-1}$ neostigmine *iv* were administered to antagonise residual neuromuscular block.

Correlation of the TOF ratio to the $DBS_{2,3}$ ratio was analyzed by linear regression. A P value <0.05 was considered statistically significant. For statistical analyses, a statistical package (Stat Flex, Statview Inc., Tokyo, Japan) was used on a personal computer (PC-9821 Ne, NEC Inc., Tokyo, Japan).

Results

Patient characteristics are shown in the Table.

The presence of fade or waxing in response to $DBS_{2,3}$ was assessed manually 150, 102, 112, 120, 96, 128, and 100 times, when the TOF ratios were 0–0.40, 0.41–0.50, 0.51–0.60, 0.61–0.70, 0.71–0.80, 0.81–0.90, and 0.91–1.00, respectively.

Figure 2 shows the probabilities in which fade and waxing in response to the $DBS_{2,3}$ could be identified manually at varying TOF ratios.

As shown in Figure 3, a strong linear correlation existed between the TOF ratio and $DBS_{2,3}$ ratio ($P <$ 0.000001). This high degree of correlation was represented by r value of 0.96 for the TOF ratio versus the $DBS_{2,3}$ ratio. The regression line was estimated:

$$\text{TOF ratio} = 0.718 \times DBS_{2,3} \text{ ratio} - 0.057$$

In no patient did the peripheral skin temperature of the investigated arm decrease below 33°C.

In each patient, after administration of the reversal agents, TOF ratio became >0.80, and tracheal extubation was performed.

TABLE Patient characteristics

n	*Sex M/F*	*Age (yr)*	*Height (cm)*	*Weight (kg)*
40	20/20	46.8 ± 7.4	164.8 ± 6.0	57.7 ± 5.0

Values are number or mean ± SD.

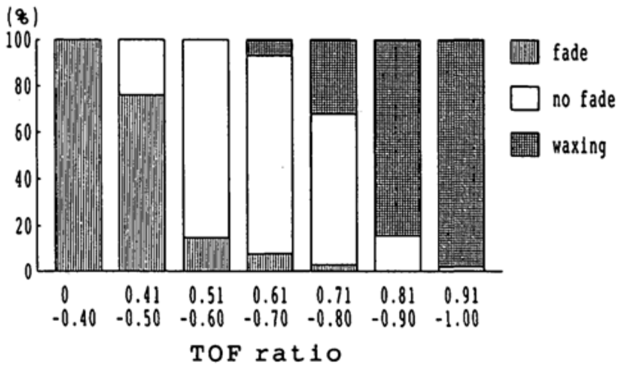

FIGURE 2 Probability of manual detection of fade and waxing in response to $DBS_{2,3}$ at varying levels of TOF ratio.

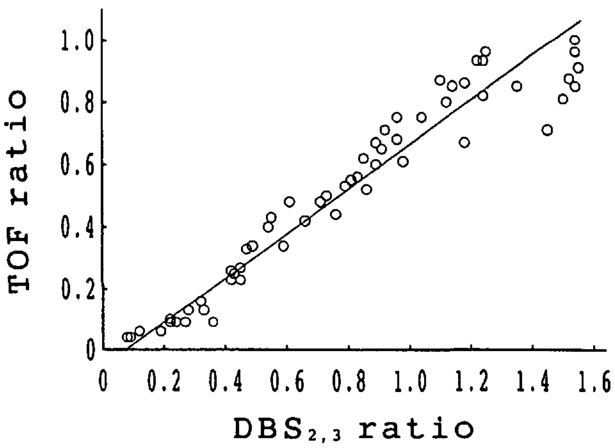

FIGURE 3 Correlation of TOF ratio to $DBS_{2,3}$ ratio (r = 0.96). The straight line represents the best-fit line. The regression line was estimated:

TOF ratio = 0.718 × $DBS_{2,3}$ ratio – 0.057.

Discussion

DBS consists of two burst stimuli separated by 750 msec. The numbers of short tetanic stimuli in the first and second in $DBS_{3,3}$ are three and three, respectively. Those in the first and second in $DBS_{3,2}$ are three and two, respectively. The response to DBS is two single separated muscle contractions. To evaluate depths of neuromuscular block presence or absence of fade in response to DBS is assessed by tactile means. $DBS_{3,3}$ is more sensitive than TOF for clinical assessment of recovery from neuromuscular block,[1–5] and in addition, $DBS_{3,2}$ is more sensitive than $DBS_{3,3}$.[1–3] A at a TOF ratio of 0.71–0.80, fade in response to $DBS_{3,3}$ stimulation is identified tactilely in only 24% of patients.[1] Thus, using $DBS_{3,3}$, adequate recovery from neuromuscular block can not be diagnosed. On the contrary, even when the TOF ratios return to 0.81–0.90 and 0.91–1.00, fades in response to $DBS_{3,2}$ are felt in as many as 63% and 33% of patients, respectively.[1] Thus, using $DBS_{3,2}$, a false impression of persistent residual neuromuscular block may arise.

The present study shows that the fade in response to $DBS_{2,3}$ stimulation pattern is identified when the level of residual neuromuscular block is still deep, and the fade becomes impalpable as the degree of block subsides. Further, the waxing in response to the $DBS_{2,3}$ stimuli was felt when a sufficient level of recovery had been reached.

The probability of tactile detection of fade in response to the $DBS_{2,3}$ was as high as 100 and 76% when the TOF ratios were 0–0.40 and 0.41–0.50, respectively, however, they were as low as 15, 9, 3, 0, and 0% at TOF ratios of 0.51–0.60, 0.61–0.70, 0.71–0.80, 0.81–0.90, and 0.91–1.00, respectively. A TOF ratio of 0.74 correlates well with signs of adequate clinical recovery of neuromuscular transmission.[6] Accordingly, because the fade in response to the $DBS_{2,3}$ can rarely be identified at a TOF ratio ≥0.51, the presence of fade in response to the $DBS_{2,3}$ does not indicate adequate level of recovery from neuromuscular block. Waxing in response to the $DBS_{2,3}$ was detected manually in only 0, 6, and 32% of patients when the TOF ratios were 0.00–0.60, 0.61–0.70, and 0.71–0.80, respectively, but was felt in as high as 84 and 98% of patients when the TOF ratios were 0.81–0.90 and 0.91–1.00, respectively. The present study demonstrates that the waxing response to the $DBS_{2,3}$ is detected at a high rate only when the TOF ratio ≥0.81, suggesting that the presence of waxing in response to $DBS_{2,3}$ is indicative of adequate recovery from neuromuscular block.

Brull *et al.*[4] demonstrated strong linear correlations between the TOF and the $DBS_{3,3}$ ratios, and the TOF and the $DBS_{3,2}$ ratios. The present study shows that there is a strong linear correlation also between the TOF ratio and the $DBS_{2,3}$ ratio.

In this study TOF stimuli were applied every 20 sec for more than five minutes, and 20 seconds after the preceding TOF stimulation, $DBS_{2,3}$ was delivered. Twenty sec after the $DBS_{2,3}$, TOF stimuli were again applied every 20 sec. It was noted that TOF stimuli should be repeated not more frequently than once every 10 sec.[8,9] However, Meretoja *et al.*[10] compared onset time and degree of maximum neuromuscular block after administration of an ED_{50} doses of atracurium, vecuronium, or mivacurium when TOF stimulation was given once every 10 sec or 20 sec, and showed that the onset time was shorter and the degree of maximum block was greater when TOF stimuli were given every 10 sec. In the present study, TOF stimuli were repeated every 20 sec, so the TOF-induced overestimation of the depth of neuromuscular block might be of little importance. In previous studies[2,3] DBS stimuli were repeated every 20 sec. Engbæk *et al.*[1] reported that increases in TOF ratio 15 sec and 27 sec after DBS was only one percent and one percent, respectively, but the increases were different from the TOF ratio obtained before the DBS. Hence, strictly speaking, the time interval between the DBS and TOF stimulation should be >27 sec.

$DBS_{2,3}$ stimuli were delivered simultaneously to the control arm and test arm in this study. The mechanical TOF ratio recorded 20 sec before $DBS_{2,3}$ was regarded as the TOF ratio at which an observer felt fade, no fade, or waxing in response to $DBS_{2,3}$. In the present study vecuronium was administered continuously to maintain a stable degree of neuromuscular block for five minutes, so the $DBS_{2,3}$ ratio would correspond well with the TOF ratio obtained 20 sec before the $DBS_{2,3}$. However, to establish a proper relationship between the $DBS_{2,3}$ and TOF ratios, $DBS_{2,3}$ stimulation should have been applied simultaneously with TOF stimulation.

During evaluation of fade in response to $DBS_{2,3}$, the four ulnar fingers were immobilised in the control arm, but the four ulnar fingers and thumb were free in the test arm. No previous study compared the probability of detection of fade when the four ulnar fingers were kept immobilised and when the fingers were free. However, Drenck *et al.*[5] showed that when the fingers were kept immobilised the probabilities of manual detection of fades in response to TOF stimulation were about 21% and 1% at mechanical TOF ratios of 0.41–0.50 and 0.61–0.70, respectively. In contrast, Viby-Mogensen *et al.*[11] demonstrated that when the fingers were free the probabilities of manual detection of fades in response to TOF stimulation were as many as 56% and 35% at mechanical TOF ratios of 0.41–0.50 and 0.61–0.70, respectively. In the two previous studies moderately experienced observers evaluated the presence or absence of fade by tactile means. Therefore, if the four ulnar fingers are free, fades may more readily be identified manually.

In conclusion, $DBS_{2,3}$ is of use because when residual neuromuscular block is clinically important, fade is identified, but when neuromuscular function has returned to an adequate level, waxing can be detected.

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