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Vecuronium Neuromuscular Blockade at the Diaphragm, the Orbicularis Oculi, and Adductor Pollicis Muscles

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To determine the relationship among diaphragm, orbicularis oculi, and adductor pollicis blockade, train-of-four stimulation was applied to the phrenic, facial, and ulnar nerves in 16 adult patients anesthetized with alfentanil–propofol–oxygen. Vecuronium 0.04 or 0.07 mg/kg was given. The response of the adductor pollicis was measured with a force transducer, and that of the other muscles by electromyography (EMG). No statistically significant differences were detected with either dose in the intensity of maximum blockade measured at the three muscles. With 0.04 mg/kg, the first response (T1) in the train-of-four was decreased (mean ± SEM) 78 ± 8, 62 ± 11, and 84 ± 3% for the diaphragm, orbicularis oculi, and adductor pollicis, respectively. Corresponding values after 0.07 mg/kg were 95 ± 3, 82 ± 11, and 95 ± 2%, respectively. However, onset time was longer at the adductor pollicis than at the diaphragm, and the orbicularis oculi onset time approached that of the diaphragm. With 0.04 mg/kg, time to maximum diaphragmatic blockade was 2.9 ± 0.3 min, compared with 3.7 ± 0.6 min at the orbicularis oculi (no significant difference [NS]) and 6.6 ± 0.4 min at the adductor pollicis ($P < 0.001$). With vecuronium 0.07 mg/kg the values were 2.2 ± 0.3, 3.4 ± 0.5 ($P = 0.024$), and 6.3 ± 0.6 ($P < 0.001$), respectively. Time to 75% T1 recovery was similar at the diaphragm and the orbicularis oculi, but significantly longer at the adductor pollicis. The values were 14.6 ± 2.4, 17.8 ± 5.2 (NS), and 24.0 ± 2.8 min ($P = 0.01$), respectively, after 0.04 mg/kg, and were 26.0 ± 4.0, 28.7 ± 4.1 (NS), and 35.2 ± 4.0 min ($P = 0.005$), respectively, after 0.07 mg/kg. It is concluded that the orbicularis oculi response to facial stimulation reflects the extent of neuromuscular blockade of the diaphragm better than does the response of the adductor pollicis to ulnar nerve stimulation. **(Key words: Monitoring, neuromuscular blockade. Neuromuscular relaxants: vecuronium. Skeletal muscle: adductor pollicis; diaphragm; orbicularis oculi.)**

THE RESPONSE of the diaphragm neuromuscular junction to nondepolarizing relaxants is different from that of the adductor pollicis muscle, both in intensity and in time course. The cumulative dose–response curve for the diaphragm is shifted to the right compared to that of the adductor pollicis, for pancuronium,[1] atracurium,[2] and vecuronium.[2,3] The dose required for 90% blockade has been reported to be 40–100% greater for the diaphragm than for the adductor pollicis.[1–3] This difference in sensitivity may explain the earlier recovery of the diaphragm.[4,5] However, onset of neuromuscular blockade occurs earlier at the diaphragm.[4,5] This is believed to be due to differences in blood flow and early distribution of the relaxant. Thus, there are wide discrepancies between adductor pollicis and diaphragm blockade, both in intensity and time course.

Monitoring neuromuscular blockade of the diaphragm by stimulating the phrenic nerve is not practical clinically. Thus, a more accessible muscle with similar onset time, maximum blockade and recovery would be an asset. The orbicularis oculi muscle has been found to recover more rapidly from neuromuscular blockade than does the adductor pollicis.[6,7] However, characteristics of onset of blockade are not known, and the maximum response to subparalyzing doses of nondepolarizing relaxants has not been measured.

The purpose of this study was to examine the relationship among the diaphragm, orbicularis oculi, and adductor pollicis muscles during onset and recovery after a single dose of vecuronium. In all cases, the response of the muscle was measured after train-of-four stimulation of the corresponding nerve. Two doses of vecuronium were chosen—0.07 mg/kg, which is expected to abolish diaphragmatic response in most individuals,[2,3] and 0.04 mg/kg, which is approximately equal to ED_{95} for the adductor pollicis.[8]

Methods

The protocol was approved by the institution's Ethics Committee, and informed consent was obtained from the subjects. Sixteen adult patients scheduled for diagnostic laryngeal and pharyngeal endoscopy were included in the study. Individuals with clinical or radiologic evidence of upper airway obstruction were excluded, as were those with previous head and neck surgery, radiotherapy, or chemotherapy. Patients with cardiac, respiratory, or neuromuscular disease also were excluded. Other exclusion criteria were malnutrition, excessive alcohol intake, and concurrent administration of any medication known or suspected to interfere with neuromuscular function. The patients' demographic data are presented in table 1. Those who received the larger dose of vecuronium (0.07 mg/kg) were slightly taller and heavier than those of the other

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TABLE 1. Demographic Data

Dose (mg/kg)	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)
0.04	7/1	54 ± 4	59 ± 5	166 ± 3
0.07	8/0	52 ± 5	66 ± 3	176 ± 2

Mean ± SEM when applicable.

group (0.04 mg/kg). There was no age difference between the groups.

The patients received diazepam 5–10 mg 1 h before the scheduled start of the procedure. On arrival in the operating room, ECG and noninvasive blood pressure monitors were attached. Anesthesia was induced with alfentanil 20–30 μg/kg and propofol 2–3 mg/kg intravenously. Then, depending of the type of surgery, either a cricothyroid membrane puncture was performed to permit jet ventilation, or tracheal intubation was performed, without the use of muscle relaxants. Anesthesia was maintained with an infusion of propofol at a rate of approximately 10 $mg \cdot kg^{-1} \cdot h^{-1}$ and intermittent doses of alfentanil. No muscle relaxant was given during endoscopy. After endoscopy, tracheal intubation was performed in the patients who had received jet ventilation. The lungs of all patients were mechanically ventilated, and 100% oxygen was administered. The propofol infusion was continued. End-tidal CO_2 was monitored, and ventilation was adjusted to maintain normocapnia (35–40 mmHg).

Surface electrodes were applied to the ulnar nerve at the wrist, to the right phrenic nerve at the base of the neck,[1,2] and to the temporal branch of the right facial nerve, anterior to the ear lobe. The force of contraction of the adductor pollicis muscle was recorded with a Bio-industry Curametre Module 2 Transducer. Diaphragmatic response was evaluated by measuring the size of the electromyographic (EMG) signal obtained by two surface electrodes located in the eighth or ninth intercostal space in the anterior and midaxillary lines, respectively.[1,2] Two surface electrodes were also applied near the medial border and the central portion of the eyebrow, respectively, to measure the activity of the orbicularis oculi muscle. Both EMG signals were amplified with a Dantec type I5CO1 EMG amplifier. The responses of all three muscles were displayed on a Gould V1000 CRT and recorded simultaneously on paper with a Gould ES1000 chart recorder.

Before injection of vecuronium, supramaximal stimulation was obtained with three Bio-industry Curamatre stimulators, which deliver 0.2-ms impulses, with constant current of up to 70 mA. The diaphragmatic response was judged adequate when the EMG signal was maximal, reproducible, and corresponded to a hiccuping movement. Currents in the range of 60–70 mA usually were required, and brachial plexus movement was avoided. To stimulate the orbicularis oculi, the electrodes were applied at the location that produced maximal orbicularis oculi movement with the least movement of other facial muscles. This location was variable, but was usually 2–3 cm anterior to the ear lobe. The electrodes were placed 1–2 cm from each other. Typically, the EMG response was biphasic, its amplitude was 0.5–1.0 mV and its duration 5–10 ms (fig. 1). Supramaximal stimulation was usually obtained with currents of 15–25 mA. Confirmation that the EMG signals obtained corresponded to the mechanical action was obtained by visual inspection. During paralysis, the number of twitches observed was verified to be the same as the number of signals obtained on the tracing. Direct muscle stimulation was ruled out because the response was abolished by large doses of vecuronium.

Supramaximal train-of-four stimulation was applied every 10 s at all three nerves and baseline response recorded for 2–3 min. Then, vecuronium 0.04 or 0.07 mg/kg was administered as a rapid bolus. Eight patients received each dose. The interval between train-of-four stimulation was increased to 20 s after maximum blockade was observed. Neuromuscular blockade was measured as the decrement in contractile response or amplitude of EMG response of the first response to train-of-four stimulation (T1), relative to control. Similarly, the train-of-four ratio (T4/T1), the ratio of the fourth to the first response, was measured. These measurements were made

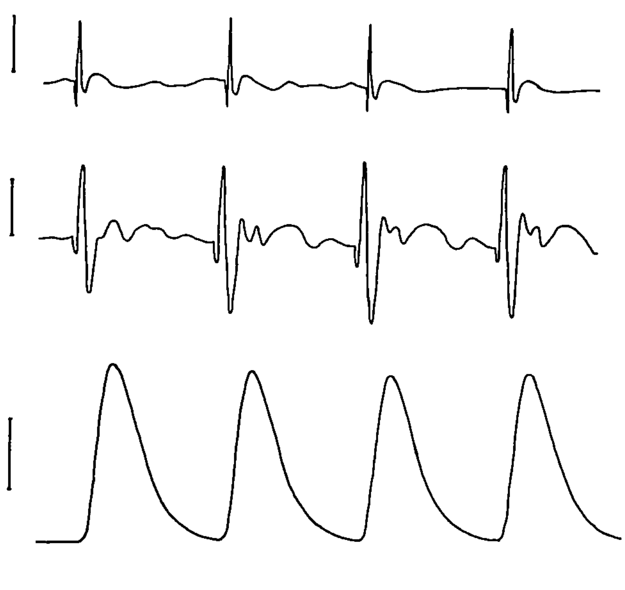

FIG. 1. EMG tracings of train-of-four responses at the orbicularis oculi (*top*) and at the diaphragm (*middle*). Force of contraction of the adductor pollicis is also shown (*bottom*). No vecuronium given. Time scale = 200 ms; EMG (*top* and *middle*) = 500 μV; force of contraction = 500 g.

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until at least 70% recovery of T4/T1 was reached at all three muscles. Also measured were the following: the times to 5%, 50%, and maximum T1 blockade; the intensity of maximal blockade; and the times from injection to 25 and 75% T1 recovery.

To determine the extent to which the orbicularis oculi and adductor pollicis blockade correlated with diaphragmatic paralysis, the T1 response of each muscle was plotted against T1 of the diaphragm, for each patient, both for onset and recovery. The area between the onset and recovery curves was considered to be a measure of the discrepancy between the two responses. The same analysis was performed for the T4/T1 response.

Unless otherwise specified, the results are presented as means ± standard error of the mean (SEM). Paired comparisons were made between the diaphragm response and either the orbicularis oculi or the adductor pollicis. Student's *t* test for paired data was used, with Bonferroni correction for multiple comparisons. A P value of less than 0.05 was considered to indicate a statistically significant difference.

Results

In both study groups, both onset and recovery were statistically more rapid at the diaphragm than at the adductor pollicis (tables 2 and 3 and figs. 2 and 3). Maximum blockade was not statistically different when both muscles were compared (table 2). With the vecuronium dose of 0.07 mg/kg, 100% diaphragmatic blockade occurred in five of eight patients. The same dose produced complete adductor pollicis blockade in only two patients. With 0.04 mg/kg, no patient exhibited 100% blockade at either muscle.

Blockade at the orbicularis oculi muscle appeared to be only slightly slower than at the diaphragm, and statistical significance was achieved only for maximum blockade after a 0.07 mg/kg dose (table 2). Maximum blockade was not statistically different between the two muscles (table 2). Complete neuromuscular blockade was found in none of the patients who received 0.04 mg/kg and in three of the patients who received 0.07 mg/kg. Recovery characteristics at the orbicularis oculi were similar to those of the diaphragm (table 3 and figures 2 and 3).

When the T1 response of the adductor pollicis was plotted against the T1 response of the diaphragm, a large hysteresis was found (fig. 4), because at the same intensity of diaphragmatic blockade, the adductor pollicis twitch height was much greater during onset than during recovery. This hysteresis was much less ($P < 0.001$ for both doses of vecuronium) when the orbicularis oculi T1 was plotted against diaphragmatic blockade (fig. 5).

T4/T1 decreased more slowly than did T1 at all three muscles during onset and took more time to recover. Again, the orbicularis oculi response was a better reflection of diaphragmatic paralysis than was the adductor pollicis. The curves of orbicularis oculi *versus* diaphragm T4/T1 showed less hysteresis than did those of adductor pollicis *versus* T4/T1 ($P < 0.001$ for both doses).

TABLE 2. Onset Characteristics for T1

Dose (mg/kg)	Muscle	Maximum Blockade (% of control)	Time to Maximum Blockade (min)
0.04	Diaphragm	77 ± 9	2.9 ± 0.6
	Orbicularis	63 ± 13	3.8 ± 0.6
	Adductor	83 ± 4	6.8 ± 0.5*
0.07	Diaphragm	95 ± 3	2.2 ± 0.3
	Orbicularis	82 ± 11	3.4 ± 0.5*
	Adductor	95 ± 2	6.3 ± 0.6*

Mean ± SEM.
* $P < 0.05$.

TABLE 3. Recovery Characteristics for T1

Dose (mg/kg)	Muscle	Time to 25% (min)	Time to 75% (min)
0.04	Diaphragm	†	14.8 ± 3.0
	Orbicularis	†	17.6 ± 8.0
	Adductor	†	24.5 ± 5.0*
0.07	Diaphragm	15.6 ± 2.5	26.0 ± 4.0
	Orbicularis	18.0 ± 2.7	28.7 ± 4.1
	Adductor	20.6 ± 2.6*	35.2 ± 4.0*

Mean ± SEM.
* $P < 0.05$ when compared with the diaphragam.
† Many patients did not reach 75% blockade.

Discussion

This study showed that after the injection of vecuronium 0.04 or 0.07 mg/kg the orbicularis oculi was a better

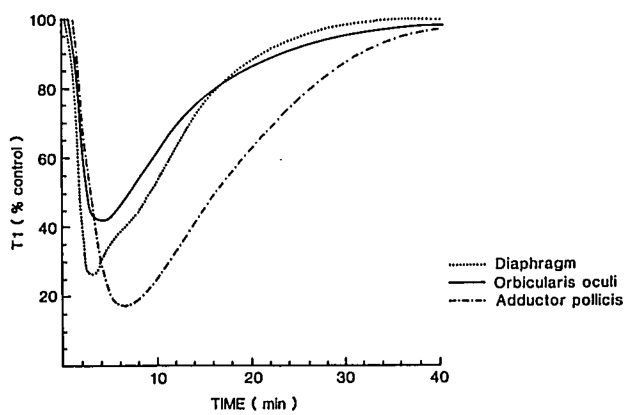

FIG. 2. T1 in the train-of-four obtained at the three muscles after vecuronium 0.04 mg/kg. Standard errors omitted for the sake of clarity.

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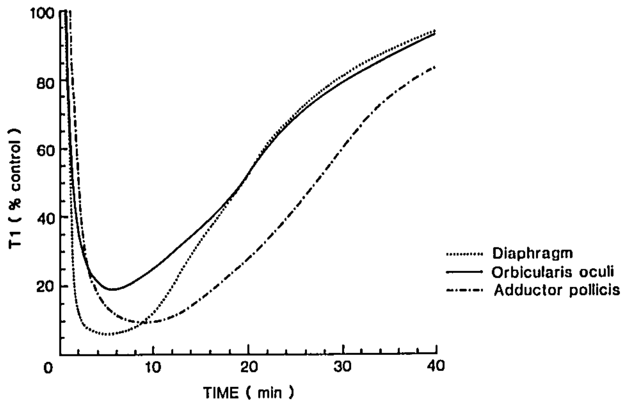

FIG. 3. T1 in the train-of-four obtained at the three muscles after vecuronium 0.07 mg/kg. Standard errors omitted for the sake of clarity.

reflection of diaphragmatic paralysis than was the adductor pollicis, both during onset of blockade and recovery. No statistically significant difference among the three muscles was found in the maximum intensity of blockade. However, onset occurred later at the adductor pollicis (6–7 min) than at either the diaphragm (2–3 min) or the orbicularis oculi (3–4 min). Neither inhalational agents nor nitrous oxide were given.

These results support the previous findings that diaphragmatic paralysis occurs sooner than does adductor pollicis blockade.[4,5] In the current study, maximum diaphragmatic blockade occurred later (2–3 min) than it did in the previous study (1–2 min),[4] because of the smaller dose given. Recovery from diaphragmatic blockade oc-

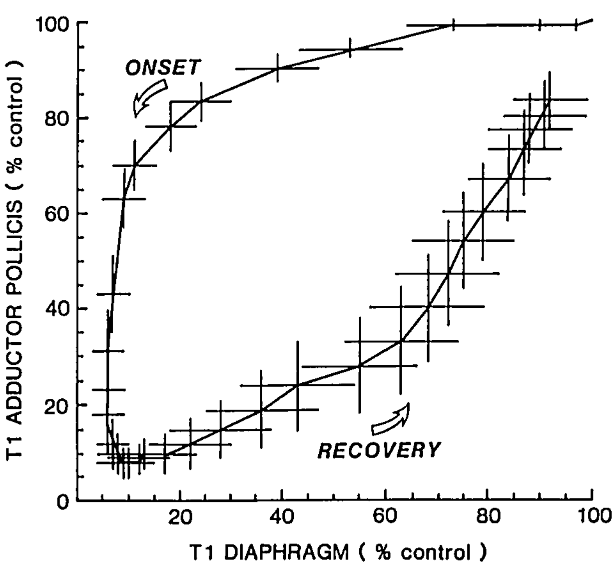

FIG. 4. T1 of the adductor pollicis *versus* T1 of the diaphragm, after vecuronium 0.07 mg/kg. Bars represent SEM.

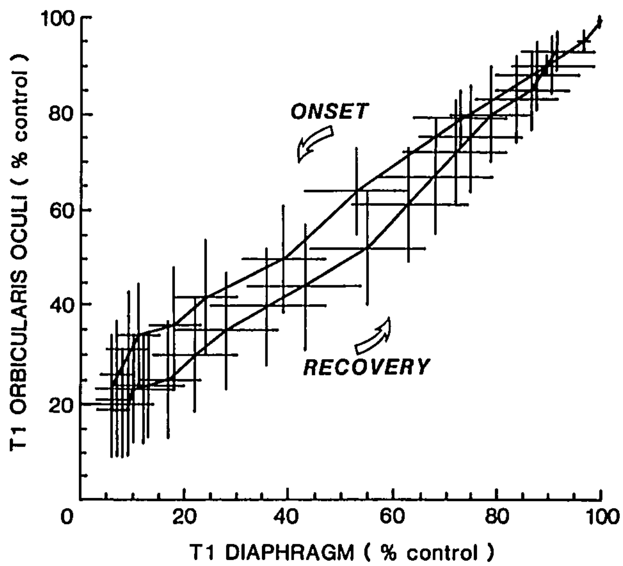

FIG. 5. T1 of the orbicularis oculi *versus* T1 of the diaphragm, after vecuronium 0.07 mg/kg. Bars represent SEM.

curred sooner than did adductor pollicis recovery; this finding is in agreement with previous studies.[4–5] Since termination of effect is governed largely by the rate of decrease in plasma concentrations,[9] the vecuronium concentrations associated with a given degree of blockade are probably larger for the diaphragm than for the adductor pollicis. This different concentration–response relationship accounts for the "diaphragm sparing."[1–3,10–12] The similarity between orbicularis oculi and diaphragm blockades suggests that these muscles have nearly identical responses to the same concentration of vecuronium.

In contrast to recovery data, when diaphragmatic blockade was markedly less than adductor pollicis blockade, no difference was demonstrated in the maximum neuromuscular blockade between these muscles. This effect may be related to the faster onset of blockade at the diaphragm, which is due to a greater muscle blood flow.[4,5,9] As a result, more drug is allowed to reach the diaphragm, leading to higher peak concentrations at the neuromuscular junction, as compared to the adductor pollicis. This preferential delivery of drug would compensate for the greater vecuronium concentration required by the diaphragm for a given degree of blockade.

The data suggest that dose–response relationships obtained with single doses of vecuronium would be similar at the diaphragm and at the adductor pollicis. When two muscles with different onset times are studied, dose–response curves constructed with single doses are probably more accurate than are cumulative dose–response curves in predicting the maximal effect of one dose. In contrast, clear differences between diaphragm and adductor pollicis responses have been shown by studies on cumulative dose–

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response.[1-3] These differences were found also during recovery in the current and in previous[4-5] studies, suggesting that cumulative dose–response curves are good predictors of steady state or pseudo-steady state behavior.

The onset of neuromuscular blockade is affected also by the duration and type of stimulation used, probably through induced changes in blood flow.[13] In the current study, the stimulation pattern was the same for all three muscles tested. Therefore, although the measured onset time probably would have been longer in unstimulated muscle, the direction of change was likely to be the same in all muscles.

A force transducer was used to measure the effect of vecuronium on the adductor pollicis muscle because the transducer is considered the standard means for assessment of the effect of muscle relaxants. EMG was preferred for the other muscles because of convenience. The force of contraction of the diaphragm is normally assessed by measuring transdiaphragmatic pressure; this involves the careful positioning of a gastric tube with two pressure ports. In addition, these measurements depend on functional residual capacity (FRC)[14] and must ideally be made with a closed airway during apneic conditions. In this respect, EMG recordings are more convenient and less invasive. The EMG signal has been found to correlate well with the transdiaphragmatic pressure change in two different settings.[3,15]

The activity of the orbicularis oculi muscle was measured also by EMG. A force transducer has been used previously to make these measurements,[7] but the device was not available to us. The upper portion of the orbicularis oculi muscle lies over the lower edge of the frontal bone. Two electrodes were placed near the mid-portion of the muscle and close to its insertion, respectively, as is customary in EMG. Other muscles of facial expression probably contributed only insignificantly to the signal, because stimulation was made as selectively as possible, and the recording electrodes were located close to each other.

The current study examined the effects of train-of-four stimulation. In all three muscles studied, fade was more pronounced during recovery than during onset, and during onset higher doses produced less fade for an identical degree of first-twitch depression. In this respect, the diaphragm and the orbicularis oculi were qualitatively similar to the adductor pollicis.[16,17]

The current study suggests that monitoring orbicularis oculi may have a role in clinical practice. Since response of the orbicularis oculi is a good reflection of diaphragmatic paralysis, it appears to be preferable to the adductor pollicis in predicting the possibility of hiccups and in pushing the abdominal contents. In addition, since the diaphragm is probably the muscle of respiration that is most resistant to muscle relaxants, blockade of the diaphragm probably implies blockade of abdominal and intercostal muscles.[18,19] Thus, because train-of-four stimulation can be repeated every 10 s, facial nerve stimulation appears preferable to the use of post-tetanic count (PTC) at the adductor pollicis for the assessment of profound blockade.[20,21] The major drawback of the technique is that PTC cannot be repeated more often than every 5 min.

The onset characteristics of the orbicularis oculi blockade suggest that facial nerve stimulation can also be used to determine the optimal time to intubation. Ideal intubating conditions depend on adequate relaxation of respiratory and upper airway muscles. Onset of blockade has been measured in the masseter,[22] the laryngeal muscles,[23] and the diaphragm, and has been found to be of shorter duration in these muscles than in the adductor pollicis. Since the time course of orbicularis oculi blockade approaches that of the diaphragm, it is probably a good reflection of the time course of paralysis of other respiratory and upper airway muscles as well. Since the sensitivity of the diaphragm to relaxants is probably less than that of other muscles,[18,19] paralysis of the orbicularis oculi probably indicates complete blockade of all muscles the relaxation of which is required for adequate intubating conditions. This hypothesis needs confirmation in the clinical setting, with special emphasis on the correlation between visual and EMG assessment of orbicularis oculi responses.

Although orbicularis oculi monitoring may be valuable for monitoring the onset of relaxation and for maintenance of profound blockade, the adductor pollicis probably is preferable for the management of recovery. Respiratory variables have been correlated with adductor pollicis response.[24] The earlier recovery of the orbicularis oculi suggests that even with a T4/T1 of 100% at that muscle, residual weakness may be present, because respiratory function also depends on muscles other than the diaphragm, and these muscles may be more sensitive to the effects of neuromuscular blocking drugs.[18,19]

The close relationship between orbicularis oculi and diaphragm blockade, both in intensity and time course, suggests that the monitoring of the former may be a good guide of diaphragmatic blockade. Its monitoring is easy to perform clinically and should be considered whenever profound neuromuscular blockade is desired.

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