
The search for an optimal interval between pretreatment dose of d-tubocurarine and succinylcholine

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A study was conducted to determine the optimal interval between the administration of d-tubocurarine (dTc) and succinylcholine (SCh) with regard to onset and duration of neuromuscular block and presence of fasciculations and postoperative myalgias.

Forty female patients received dTc 3 mg·70 kg⁻¹ prior to SCh 1.5 mg·kg⁻¹. The interval between drugs was 0, 1, 3, 5, or 7 minutes. Transduced thumb adduction recorded block onset and recovery. Fasciculations were visually detected. Myalgias were assessed on postoperative interview.

Pretreatment interval did not affect the onset or recovery of neuromuscular block. Postoperative myalgias were also independent of pretreatment timing. Fasciculations were blocked with 3, 5, or 7 minute intervals, but not with 0 or 1 minute intervals. Therefore, three minutes appear to be the optimal time interval between administration of dTc and SCh since shorter intervals do not inhibit fasciculations and longer intervals do not afford any additional advantages.

Key words

NEUROMUSCULAR RELAXANTS: d-tubocurarine, succinylcholine; MUSCLE RELAXANTS: fasciculation.

Pretreatment drugs are given prior to succinylcholine (SCh) to prevent or diminish its side effects. The claimed benefits of pretreatment include attenuated rises in intra-ocular, intra-gastric, and intra-cranial pressures, decreased rises in serum potassium concentration, and a decreased incidence and severity of fasciculations and postoperative myalgias.

Agents used for pretreatment include small doses of SCh,¹ lidocaine,^{2,3} diazepam,⁴⁻⁶ vitamin C,⁷ and the nondepolarizing muscle relaxants.⁸⁻¹² Whereas numerous investigations have explored the efficacy of the nondepolarizing relaxants, little attention has been directed to the optimum time interval between administration of the pretreatment agent and SCh.

While three minutes is commonly taught as the appropriate time interval between non-depolarizing relaxant and SCh, the authors have noted that practicing anaesthetists pay little regard to the exact timing. As a result, intervals range from a few seconds to over ten minutes with apparent clinical success, but without documentation in the literature.

Only one study compared onset and recovery from paralysis with two different time intervals;⁸ no difference was found. However, the data may not be valid because crude measurement techniques were employed. In addition that study found a delayed onset and no hastening of recovery of block with pretreatment, the opposite of what subsequent multiple investigations have concluded. For these reasons, the authors re-examined the issue of pretreatment timing interval.

We studied the effects of a varying interval

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between administration of d-tubocurarine (dTc) and SCh on the onset of paralysis, the recovery from paralysis, the occurrence of fasciculations, and the frequency of postoperative myalgias. We hoped to find an optimal time interval for the parameters measured, or validate the practice of total disregard for the interval.

Methods

This investigation was approved by our institution's Committee for the Protection of Human Subjects from Research Risks.

Forty nonpregnant female patients who were to undergo gynecologic surgery or knee arthroscopy were divided randomly into five groups of eight patients. All patients were of ASA physical status classification I or II. No patient had a history of neurologic or muscular disease or received medications known to interact with muscle relaxants. Each patient received an induction dose of thiopentone intravenously and nitrous oxide in oxygen by face mask, and intravenous narcotic or barbiturate as needed to maintain anaesthesia. Halogenated anaesthetics were not administered.

After induction of anaesthesia, force of thumb adduction at the proximal phalanx was measured with a Grass FT 10 transducer. The ulnar nerve was stimulated at the wrist with supramaximal pulses of 200 microsecond duration at one second intervals. Use of 1 Hz stimuli permitted more precise determination of the onset of block, compared with slower rates of stimulation. While data collected using 1 Hz stimuli may differ from those using other rates, all comparisons among the data remain valid; thus the additional precision afforded by 1 Hz justifies its use.

When a suitable baseline twitch was obtained on a Grass Model 7 polygraph, d-tubocurarine $0.043 \text{ mg}\cdot\text{kg}^{-1}$ ($3 \text{ mg}\cdot 70 \text{ kg}^{-1}$) was injected into a rapidly flowing intravenous line. Group A patients received SCh $1.5 \text{ mg}\cdot\text{kg}^{-1}$ IV immediately after dTc. Other groups received SCh $1.5 \text{ mg}\cdot\text{kg}^{-1}$ IV after a specified interval: one minute for group B, three minutes for Group C, five minutes for Group D, and seven minutes for group E. Twitch tension was recorded continuously until complete recovery from SCh was achieved.

After administration of succinylcholine, the patient's eyes, neck, and extremities were observed for the presence of fasciculations. Fasciculations

were classified as follows: none = no visible fasciculations; mild = fine fingertip motion or moderate palpebral motion; moderate = minimal contractions at the neck or extremities; severe = vigorous contractions at the neck or extremities. Upon disappearance of twitch tension, laryngoscopy and tracheal intubation were performed. The presence or absence of jaw relaxation and any motion of the vocal cords were noted by the anaesthetist.

Polygraph recordings were analyzed to determine the time from administration of SCh to 95 per cent twitch depression, and the times from administration of SCh to 25 per cent recovery and 75 per cent recovery of twitch tension.

All patients were interviewed by one of the authors between 24 and 48 hours postoperatively. Each patient was asked, "Do you have any discomfort?" Then, "Do you have any aches or pains?" Postoperative myalgias were judged present or absent based upon the subsequent discussion. Discomfort from diaphragmatic irritation from residual gas insufflated during laparoscopy was excluded.

Groups were examined for differences in age, body weight, kind of surgery, fasciculation score, incidence of postoperative myalgias, time to 95 per cent block, time to 25 per cent recovery, time to 75 per cent recovery, and 25 per cent–75 per cent recovery time. Analysis of variance or the Chi-square contingency test was used. Differences were deemed significant if at the $p < 0.05$ level. Fasciculation data were subjected to the Jonckheere-Terpstra nonparametric test for ordered alternatives.¹³

Results

Each group contained eight patients. The groups were similar with respect to age, body weight, and kinds of surgery (Table I). All patients had adequate jaw relaxation and motionless vocal cords during laryngoscopy. All patients were ambulating by the first postoperative day.

Times to onset of paralysis and recovery from neuromuscular block appear in Table II. The groups did not differ in time to 95 per cent block, time to 25 per cent recovery, time to 75 per cent recovery, or time from 25 per cent to 75 per cent recovery.

Fasciculation scores appear in Table III. The Jonckheere-Terpstra test showed a decreasing severity of fasciculations with increasing interval

TABLE I Patient demographic data

Group	A	B	C	D	E
Interval (mins)	0	1	3	5	7
Age (years)*	31 ± 6	42 ± 21	39 ± 13	38 ± 10	30 ± 8
Weight (kg)*	70 ± 16	61 ± 10	62 ± 13	60 ± 6	60 ± 10
Kind of Surgery:†					
Laparotomy	2	3	1	1	3
Vaginal hysterectomy	1	0	1	1	0
Arthroscopic (knee)	0	1	0	1	0
Laparoscopic	5	4	6	5	5

*Mean ± SD (N = 8) p = NS among groups.

†Entries are number of patients.

between dTc and SCh significant at the $p < 0.001$ level.

Despite the difference in fasciculations, the groups did not differ significantly in the incidence of postoperative myalgias ($\chi^2 = 1.4$, $p = NS$).

Patients in each group were divided into two categories: those who underwent minor surgery (arthroscopic or laparoscopic) and those who underwent major surgery (vaginal hysterectomy or laparotomy). Two-way analysis of variance applied to the frequency of myalgias in each subgroup disclosed no effect of type of surgery or of interval of drug administration on frequency of myalgias.

Discussion

Several publications have addressed the effects of pretreatment on the onset and recovery of neuromuscular blockade. Table IV summarizes their features. The methods of these various studies differ in the use of halogenated anaesthetics, in stimulus frequency, in the technique of neuromuscular blockade measurement, in the dose of SCh, and in the interval between dTc and SCh. Nevertheless, the studies show considerable agreement in the effects on onset and recovery of block.

TABLE III Fasciculation scores and myalgia frequency

Group	A	B	C	D	E
Interval (min)	0	1	3	5	7
Fasciculation score:*					
none	0	1	5	6	7
mild	0	4	3	2	1
moderate	1	3	0	0	0
severe	7	0	0	0	0
Myalgia:*					
present	4	3	3	2	3
absent	4	5	5	6	5

*Number of patients.

Paralysis times

Pretreatment does not affect the onset of neuromuscular block.^{11,14,15} Only Cullen's study⁸ disagrees; this might be explained by the fact that Cullen did not measure twitch tension. Our results indicate no effect of intervals of 0, 1, 3, 5, or 7 minutes on onset of block.

Recovery from paralysis is hastened by pretreatment with dTc if the SCh dose is not increased.^{11,14-16} When SCh dose is increased with pretreatment, recovery from paralysis is not affected.

TABLE II Twitch tension data

Group	A	B	C	D	E	p
Interval (min)	0	1	3	5	7	
Time to 95% Block (sec)	55 ± 14*	42 ± 7	43 ± 19	41 ± 12	40 ± 9	NS
Time to 25% Recovery (sec)	465 ± 59	527 ± 150	505 ± 67	453 ± 79	571 ± 149	NS
Time to 75% Recovery (sec)	560 ± 77	628 ± 179	608 ± 69	546 ± 101	656 ± 164	NS
Time from 25% to 75% Recovery (sec)	95 ± 24	101 ± 32	103 ± 21	93 ± 31	85 ± 19	NS

*Mean ± SD; N = 8 for all entries.

TABLE IV Summary of some previous studies of pretreatment with d-tubocurarine

Authors	Stimulus frequency (Hz)	Measure-ment technique	Interval (min)	Dose SCh	Effect of pretreatment on		Comments
					Onset of block	Recovery of block	
Waltz and Dillon ¹⁴	0.25	TTA	3	40 mg·m ⁻²	Not studied	Hastened	1% Halothane
Miller and Way ¹⁵	0.25	TTA	3	1 mg·kg ⁻¹	None	Hastened	
Cullen ⁸	0.25	FF	3	1 mg·kg ⁻¹	Delayed	None	*Compared with control
			7	1.5 mg·kg ⁻¹	None*	None	group (SCh 1 mg·kg ⁻¹)
Freund and Rubin ¹⁶	0.25	TTA	4	0.7 mg·kg ⁻¹	Not studied	Hastened	†Compared with control
			4	1.2 mg·kg ⁻¹	Not studied	None†	(SCh 0.7 mg·kg ⁻¹)
Blitt <i>et al.</i> ¹¹	0.25	TTA	>3	1.5 mg·kg ⁻¹	None	Hastened‡	‡Compared with SCh 1.5 mg·kg ⁻¹ control; no effect compared with SCh 1 mg·kg ⁻¹ control

TTA = Transduced Thumb Adduction. FF = Observed Finger Flexion.

ted.^{11,16} Again, Cullen's study differs.⁸ Although Cullen found no difference between recovery times for three-minute and seven-minute intervals, the authors expected to uncover an effect of interval utilizing twitch tension measurement and intervals as diverse as zero and seven minutes. In particular, we expected group A (zero minutes) patients to demonstrate more rapid recovery, as if they had received SCh without dTc. No such effect was found, indicating that the hastening effect of dTc on recovery of SCh block is present even when dTc and SCh are administered simultaneously. We did not investigate administration of dTc after SCh to shorten the duration of SCh block; our results suggest this as a possibility, however.

Fasciculations

Virtue¹² examined the efficacy of pretreatment in blocking fasciculations using either a 30-second or 60-second time interval. SCh 60 mg·70 kg⁻¹ was given after dTc 4.5 mg. Overall, 32 per cent of his patients displayed fasciculations, 30 per cent in the 30-second group and 35 per cent in the 60-second group ($p = NS$). Our results differ: only 1 of 16 patients in our groups A and B had no visible fasciculations. We attribute this to the larger dose of SCh and smaller dose of dTc employed in the current study, as well as to the different time intervals. To prevent fasciculations, there is no advantage in waiting longer than three minutes, and some advantage to waiting more than one minute, according to our results.

Myalgias

Pretreatment interval did not affect the frequency of postoperative myalgias. Based on the difference in fasciculations among groups, one might expect myalgias to be more common in groups A and B. Several phenomena may explain the absence of myalgias despite moderate to strong fasciculations. First, lack of correlation of fasciculations with myalgias is common.¹⁷ Second, some factors known to affect myalgias were not controlled in this study: duration of operation,¹⁸ patient position,¹⁹ and the time, amount, and frequency of injection of thiopentone.²⁰ Third, dTc may protect the patient from myalgias even when administered zero or one minute prior to SCh. It is noteworthy, however, that dTc administered subsequent to SCh is ineffective in this regard.²¹

The authors selected a control group for this study from these choices: omission of pretreatment dose without modifying SCh dose; omission of pretreatment dose with reduction of SCh dose; and, not altering any relaxant drug dose but using a zero time interval.

The first choice is unsuitable because the hastening of recovery from paralysis by pretreatment^{11,14-16} will confound comparisons intended to examine the effect of interval alone. The second choice complicates matters in that different doses of SCh alone might affect onset of block, severity of fasciculations, or presence of myalgias. This study investigates the effects of pretreatment interval, not the effects of pretreatment itself; thus, the third

choice of control group was selected, one with an interval of zero minutes.

A limitation of this investigation is its single-blinded nature. However, knowledge by the investigator of group assignments could not affect the twitch data collected by polygraph. Also, fasciculation scores were defined in a manner sufficiently rigid to permit little room for interpretation and thus little investigator bias. Myalgia data are more susceptible to investigator bias. The lack of a significant effect of interval on myalgias despite an effect on fasciculations, and the agreement of this finding with previously published reports¹⁷ suggests validity of the myalgia data despite absence of a double-blinded design.

In summary, this study reaffirmed the time constraints for blocking fasciculations already known: the incidence and severity of fasciculations is reduced when the interval between dTc and SCH is three minutes or greater.

However, neither onset nor recovery of block varied with intervals ranging from zero to seven minutes. With respect to paralysis and myalgias, there is no optimum interval: simultaneous drug administration will suffice. However, if anaesthetists prefer to avoid fasciculations, a three-minute interval is superior to shorter ones; longer intervals offer no additional benefit.

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Résumé

On a cherché à déterminer l'intervalle idéal à maintenir entre l'administration préventive de la d-tubocurarine (dTc) et celle de la succinylcholine (SCh), intervalle qui permettrait de conserver la rapidité d'installation du bloc neuromusculaire et sa durée tout en minimisant les fasciculations et les myalgies post-opératoires.

L'étude a porté sur 40 patientes ayant reçu $3 \text{ mg} \cdot 70 \text{ kg}^{-1}$ de dTc avant l'administration de $1.5 \text{ mg} \cdot \text{kg}^{-1}$ SCh. Les patientes ont été réparties en groupes où l'intervalle entre l'administration des médicaments a été de 0, 1, 3, 5, et 7 minutes. La mesure de l'adduction du pouce par transducteur monitorait l'installation et la disparition du bloc neuromusculaire. Les fasciculations étaient observées visuellement et les myalgies évaluées au cours d'une entrevue post-opératoire.

L'installation ou la disparition du bloc neuromusculaire n'est pas influencée par l'intervalle entre les injections non plus que les myalgies post-opératoires. Les fasciculations étaient éliminées pour des intervalles de 3, 5 ou 7 minutes mais encore présentes pour des intervalles de 0 ou 1 minute.

Il semble donc qu'un intervalle de trois minutes entre l'administration de dTc et de SCh est souhaitable car des intervalles plus courts ne préviennent pas les fasciculations et des intervalles plus longs n'apportent aucun avantage additionnel.