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**My Patients Never Have Residual Paralysis in the PACU, or Do They?**

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**Stem Case and Key Questions Content**

You took over the medical direction of a case, a 68 year old woman undergoing a thoracic aortic aneurysm repair (endovascular) that a colleague had started with a CRNA. The patient weighed 78 kg, is 5 ft 3" tall and was intubated with 10 mg vecuronium and a sleep dose of etomidate. Everything is going well and per usual routine and when surgery is finished you are called to the room by the CRNA, to attend and participate in the emergence. On arrival to the operating room, you ask about reversal of muscle relaxation and are told that reversal has already been administered.

Please see the copy of the anesthesia record.

1. The agent analyzer shows an end-tidal concentration of volatile agent (0.1-0.2 MAC) and you expect the patient to wake up, but she "does not look right". She has an unusual movement pattern and her spontaneous respirations appear somewhat labored. Tidal volumes are 350 ml and the ET-CO2 unremarkable in the low 40s. You suspect residual paralysis and re-apply the peripheral nerve stimulator which had been removed just prior to your arrival. There are 4 thumb twitches, and there appears to be some fade.

Does this confirm residual paralysis? How common is residual paralysis? How does one diagnose residual paralysis?

2. You review the anesthetic record again. The patient had received vecuronium for intubation. Does the choice of intermediate duration muscle relaxant (rocuronium, vecuronium, atracurium, cisatracurium) have implications with regard to residual paralysis?

3. You ask the CRNA about the response to nerve stimulation prior to reversal and you are told that there were 4 twitches prior to administration of neostigmine. You ask where the twitch monitoring was done, and you are told it was performed "at orbicularis oculi". What are the implications?

4. When is a patient an outlier and how could you determine whether this patient is an outlier?

5. The fact that the patient is breathing spontaneously with normal rate and tidal volumes, what does it mean in terms of neuromuscular blockade?

6. What is an appropriate intubating dose of vecuronium for this patient? What if rocuronium was used?

7. What risk factors does she have for residual paralysis?

8. She received neostigmine. Why did it not reverse the neuromuscular block, even 20-30 minutes after administration of neostigmine?

9. Would it have been useful to administer neostigmine earlier? Would a larger dose of neostigmine have helped?

10. What is "the zone of blind paralysis"?

11. Is there a disadvantage to giving neostigmine if it is not needed, i.e. when patients have already spontaneously fully recovered?
12. How much neostigmine should be given if we decide to reverse, although the patient has four twitches with no apparent fade?
13. Why is the updated definition of residual paralysis a TOF-ratio of 0.9?
14. Assuming sugammadex becomes available, when would you definitely use sugammadex, and when would you not?

Age: 68 | Sex: F | Weight: 172.0 lb / 78.0 kg | Height: 63.0 in / 160.0 cm | BMI: 30.5 | ASA: III | Sta[redacted]2.

Procedure: ENDOVASCULAR AAA REP /MIPS/EVT/CAR STENT/PERIPHER (THORACIC ENDOVASCULAR AAA REPAIR) T.

Diagnosis: DISSECTION OF AORTA, THORACIC

Anes. Type(s): General | Allergies: Unknown

| | | 13:15 | 13:30 | 13:45 | 14:00 | 14:15 | 14:30 | 14:45 | 15:00 | 15:15 | 15:30 | 15:45 | 16:00 | 16:15 | 16:30 | 16:45 | 17:00 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DRUGS | Cefazolin - IV (200 mg/mL) | | | | | | | | 2000 | | | | | | | | |
| | Midazolam (1 mg/mL) | 2 | | | | | | | | | | | | | | | |
| | Etomidate (2 mg/mL) | 18 | | | | | | | | | | | | | | | |
| | Vecuronium (1 mg/mL) | 10 | | | | | | | | | | | | | | | |
| | Heparin (1000 units/mL) | | | | | | | | | 8000 | | | | | | | |
| | Protamine (10 mg/mL) | | | | | | | | | | | | 50 | | | | |
| | Neostigmine (1 mg/mL) | | | | | | | | | | | | 3 | | | | |
| | Glycopyrrolate (0.2 mg/mL) | | | | | | | | | | | | 0.6 | | | | |
| | Ondansetron (2 mg/mL) | | | | | | | | | | | | 4 | | | | |
| | Flumazenil (0.1 mg/mL) | | | | | | | | | | | | | | | 0.2 | |
| FLUIDS | Lactated Ringers 1000mL (1000 mL) | | | | | | | | | 700 | | | | | | | |
| | Plasma-Lyte "A" pH 7.4 1000mL (1000 mL) | | | | | | | | | 700 | | | | | | | |
| | D5W 1000mL (1000 mL) c 3 amps bicarb gtt | | | 240 | 240 | 240 | 240 | 240 ... 78 | 78 | 78 ... 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 |
| | Propofol (1000 mg) in Premix Fluid (100 mL) | | | | | | | | | | | | | | | | 50 |
| OUT-FLU | Estimated Blood Loss | | | | | | | | | 10 | | | | | | | |

| | 13:15 | 13:30 | 13:45 | 14:00 | 14:15 | 14:30 | 14:45 | 15:00 | 15:15 | 15:30 | 15:45 | 16:00 | 16:15 | 16:30 | 16:45 | 17:00 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urine Output | | | | | | | | | 250 | | | | | | | |
| Tidal Volume | 0 | 530 | 540 | 530 | 480 | 480 | 540 | 520 | 520 | 520 | 650 | 70 | 1610 | 280 | 310 | 250 |
| Peak Inspired Pressure | 0 | 27 | 25 | 24 | 21 | 22 | 25 | 25 | 24 | 24 | 25 | 9 | 33 | 8 | 8 | 7 |
| PEEP | 0 | 4 | 5 | 8 | 8 | 7 | 8 | 8 | 8 | 8 | 8 | 5 | 6 | 0 | 0 | 0 |
| SaO2-SAT | | 100 | 100 | 100 | 92 | 99 | 97 | 99 | 99 | 98 | 98 | 100 | 98 | 100 | 99 | 100 |
| ET CO2 | | 32 | 28 | 33 | 33 | 34 | 35 | 34 | 34 | 35 | 34 | 36 | 44 | 51 | 45 | 49 |
| Fi O2 | | 97 | 59 | 70 | 70 | 70 | 70 | 70 | 71 | 70 | 70 | 94 | 65 | 97 | 97 | 97 |
| Agent= | | ISO | ISO | ISO | ISO | ISO | ISO | ISO | ISO | ISO | ISO | ISO | ISO | | | |
| ET Agent | | 0.2 | 1 | 0.9 | 0.8 | 0.8 | 0.8 | 0.8 | 0.6 | 1 | 1 | 0.6 | 0.2 | | | |
| Temperature 1 | | | 29.9 | 33.1 | 37.3 | 37.4 | 36.3 | 36.5 | 36.2 | 31 | 36.3 | 30.5 | 32.4 | | | |
| EKG | | NSR | NSR | NSR | NSR | NSR | NSR | NSR | NSR | NSR | NSR | NSR | NSR | | NSR | NSR |

**Model Discussion Content**

*Incidence and definition of residual paralysis*

Residual paralysis at the time of extubation and on arrival to the PACU is a common problem. In a meta-analyis by Naguib et al(1), the pooled estimate for the incidence of residual paralysis with intermediate-acting muscle relaxants was 41.3% with a 95% CI of 25-58%. When anesthesia providers subjectively assess the twitch response of the thumb to ulnar nerve stimulation, they are not able to identify fade when the train-of-four (TOF) ratio exceeds 0.4.. That is to say, even when the amplitude of the 4th twitch is only half of the amplitude of the first twitch, and the TOF-ratio is 0.50, we perceive this as four equal twitches and fail to detect the fade (2). When using a conventional nerve stimulator, the range from 0.40 to 0.90 has therefore

been referred to as “the zone of blind paralysis”(3). If there is fade in the TOF response, then the TOF-ratio is likely to be <0.4. The current definition of residual paralysis is TOF-ratio<0.90 but we need a more sophisticated type of nerve stimulator to identify partial paralysis in the TOF-ratio range 0.4-1.0. These are called quantitative, or objective, monitors and will give us a precise measurement of the TOF-ratio. Examples of quantitative monitors include TOF-Watch® and NMT modules by GE Healthcare, Philips, and Spacelabs.

*It is not helpful to give neostigmine early*
The typical recovery and reversal of muscle relaxation consists of two components. One component is the spontaneous recovery of the NMBD which is related to its decreasing plasma concentration by way of its normal metabolism and elimination. The other is neostigmine’s inhibition of acetylcholinesterase, which allows more acetylcholine to compete with the NMBD for the nicotinic acetylcholine receptors. Neostigmine’s effect peaks at 10 minutes (4,5). Naturally, spontaneous recovery progresses continuously before and after the peak of neostigmine. Improvement in the TOF-ratio beyond neostigmine’s peak at 10 min is due to continued spontaneous recovery and hence, it is not useful to give neostigmine earlier during the course of the anesthetic. In other words, if 10 min after the administration of neostigmine, the TOF-ratio has not reached 0.90, it is unlikely that this is the result of delayed administration of neostigmine. Rather, the explanation is more likely to be that sufficient spontaneous recovery was not achieved before administration of neostigmine (6).

*Wait for TOF-count of 4 before administering neostigmine*
Many of us were taught in training to administer neostigmine with only one or two twitches present. This was appropriate when residual paralysis was defined as TOF-ratio <0.7. However, over the last 15 years a consensus has emerged that TOF-ratio ≥0.9 is necessary for adequate recovery(7,8). This has led to the updated recommendation to wait until spontaneous recovery has progressed further, i.e. at least to TOF-count of 3 and preferably 4. Kirkegaard et al elegantly showed the likely outcome from reversal at the various TOF-counts (9). When giving neostigmine with only the first twitch present, the odds of achieving a TOF-ratio of 0.9 in 10 minutes was zero and the odds of getting a TOF-ratio of at least 0.8 was 0.07. The odds of achieving TOF-ratio 0.8 in 10 minutes improved to 2.0 when delaying administration until the fourth twitch had reappeared. The odds ratio was 30, meaning that reversal to TOF-ratio 0.8 in 10 minutes was 30 times more likely when neostigmine was given with all four twitches present instead of only one twitch.

*When using neostigmine, adequate spontaneous recovery is key*
This point builds further on the previous two points. We are aware of only two studies that showed successful reversal with neostigmine to TOF-ratio 0.9 in all patients within 10 minutes. These were published by Fuchs-Buder et al (10,11), and the apparent key to this success was the extraordinary level of spontaneous recovery before the administration of neostigmine. The patients received neostigmine when the TOF-ratio was at least 0.4. As noted above, this is the degree of neuromuscular blockade when fade in the TOF can no longer be appreciated by subjective assessment.

When using a conventional nerve stimulator, attempts to reverse a deep block with neostigmine is not recommended (12). The reason for this is that neostigmine is likely to provide a partial reversal to at least TOF-ratio 0.4, at which level the clinician no longer notices any fade. We have entered the zone of blind paralysis and have no way of knowing where in the range of

TOF-ratio of 0.4-1.0 the patient may be. It has been clearly shown that reversal at a deep level of block does not get us to the goal of TOF-ratio 0.9 any sooner, it only extends the time in the zone of blind paralysis(8,13). Finally, the time to full recovery to a TOF-ratio of 0.9 is very unpredictable after such a reversal attempt.

*Inter-individual variation and outliers*
It is critical to appreciate that there is a very substantial inter-individual variation in response to NMBDs. We refer to patients who are very slow to spontaneously recover from paralysis as "outliers" and we need to treat these patients differently. We now know that these patients can be identified early during an anesthetic by simply measuring the time to return of the first twitch (14). These patients will be slow to have reappearance of all twitches and will be more difficult to reverse with neostigmine. It is also reasonable to assume that they will show increased potentiation of NMBDs by volatile agents (15) and may make good candidates for TIVA and/or reversal with sugammadex. If an outlier is to be reversed with neostigmine, this should not be attempted prior to reappearance of all four twitches, i.e. TOF-count of 4, because the time in the "zone of blind paralysis" (see above) may be substantially extended. If a quantitative monitor is used, this consideration changes as the concept of the zone of blind paralysis does not apply to quantitative monitoring.

*Don't guide reversal by monitoring of eye muscles*
A recently published study involving 150 patients documented a 5-fold increased risk of residual paralysis when TOF-monitoring was performed at the eye muscles instead of the adductor pollicis (16). More than half of patients with intraoperative twitch monitoring of eye muscles had residual paralysis on arrival to the PACU, and several patients had extremely low TOF-ratios. There are no published estimates of how common such monitoring is and no other estimates of the severity and incidence of residual paralysis with this type of monitoring. Relying on monitoring of eye muscles to guide reversal may be dangerous and Donati has stated that "reversal and recovery should be guided by adductor pollicis response, and if needed, a switch from facial to ulnar nerve stimulation should be accomplished at the end of the surgical procedure" (17).

*Avoid overdosing of NMBD by proper dose-adjustment*
NMBDs are highly charged hydrophilic molecules that should not be dosed based on total body weight (TBW). This is especially important when using rocuronium and vecuronium. A reasonable weight adjustment is to calculate ideal body weight and to add 20% of the excess weight, we can refer to this weight adjustment as "ABW20" (18). Here is an example: A female is 5'4" and weighs 200 lbs (91 kg). Her IBW is 54.7 kg (for females IBW is calculated as 45.5 kg plus 2.3 kg/inch over 5 feet). Her ABW20 is 54.7 + 0.2(91-54.7)= 62 kg. If we wish to give a full intubating dose of rocuronium 0.6 mg/kg, that would be 37 mg for this patient. In fact, a dose of 37 mg may be considered generous because it is reasonable to also dose-adjust for her being female. Several studies have shown that females require lower doses of rocuronium (19), and a further 15-20% dose adjustment may be reasonable. If the patient is elderly, a further dose adjustment is indicated (20). Finally, Kopman et al. has recommended that an appropriate routine intubating dose should be 1.5 x ED95, i.e. less than the 2 x ED95 that has often been recommended(21).

*Implement quantitative monitoring*
A quantitative monitor allows for a more sophisticated and precise management of muscle

relaxation and reversal. It has been shown (22-24) that these monitors allow for improved care. Quantitative monitors can makes it possible to identify the patients who have complete spontaneous recovery, and these patients should not be administered neostigmine. A patient who has complete spontaneous recovery is likely to become weaker if given a full dose of neostigmine(25). Finally, use of these monitors will improve our ability to use sugammadex in a targeted manner which may be cost-effective(26), at least until its price becomes less of a barrier.

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