Hypotheses & Ideas

Fade in Train Of Four: A Novel Explanation

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Abstract

A fade pattern is observed following administration of non-depolarizing neuromuscular blocking agents. However, its presence could not be easily explained after the administration of depolarizing agents. A simple description of this phenomenon is provided in the hope of better understanding and suggesting approaches for further molecular studies.

Keywords: neuromuscular junction, neuromuscular monitoring, train of four, fade, succinylcholine

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Introduction:

Nowadays, every anesthesiologist uses muscle relaxants to provide optimal surgical conditions under general anesthesia. Neuromuscular blocking agents (NMBAs), generally categorized as depolarizing NMBAs (D-NMBAs) and nondepolarizing NMBAs (ND-NMBAs), are the main implements for this purpose. To monitor the adequacy of the blockade, Train of for (TOF) is a standard technique, transferring four consecutive electrical impulses with 0.5-second intervals to a motor neuron (for instance, the ulnar nerve), which elicits a mechanical muscular response (such as thumb flexion). In anesthetized patients who do not receive NMBAs, all four responses are of the same height, and the ratio of the fourth to the first response (TOF ratio) equals 1. On the other hand, in patients who are relaxed by using ND-NMBAs, the fourth response will be less than the first one, making the ratio less than 1, a phenomenon called “fade”.

When D-NMBAs such as succinylcholine are used to provide muscle relaxation, the mechanical muscular response will decrease or diminish compared to the same patient who has not received NMBAs, but there will be no fade in TOF (i.e., the fourth response is equal to the first one despite the shorter amplitude) (1).

Different theories have been proposed to explain these fade phenomena during ND-NMBA use and the absence of fade following D-NMBAs. Some believe in the presynaptic effect of NMBAs, while others explain it with the action of voltage-gated ion channels (2, 3).

Hypothesis:

When a motor neuron is stimulated with an electrical impulse, acetylcholine (Ach) is released from the vesicles stored in the neuron ending. Usually, the released Ach and its metabolites are gathered from the neuromuscular junction and used to reproduce the new molecules and replenish the previously depleted vesicles. During TOF monitoring, the consecutive impulses do not allow the nerve ending to reuptake the Ach or its metabolites. Therefore, the nerve depends entirely on its remaining stores of Ach, decreasing

following every impulse. Based on quanta theory, about 1,000,000 Ach molecules would be released after the first impulse to activate 500,000 nicotinic receptors (nAchR) (4). With TOF monitoring, the second one arrives right after the first impulse (0.5 seconds). Thus, the ending does not have enough time to reproduce new molecules and must use its partially depleted stores. Consequently, this applies to the third and fourth impulses, and the amount of Ach molecules would be much less than the first impulse.

While there is no NMBA in the junction, the amount of released Ach molecules is adequate to elicit the response in nAchR and a normal response is detected (the muscle contracts and the TOF ratio equals 1). Adding ND-NMBAs to the junction, they compete against Ach molecules for binding to nicotinic receptors.

Here, we suggest a theoretical explanation for this "fading" phenomenon. Since the distribution of ND-NMBAs is not homogenous, one could think of all junctions in one individual muscle as below: following administration of any ND-NMBDs, some of the junctions are flooded with ND-NMBAs (A), some are less flooded (B), the third group of junctions have moderate amount of ND-NMBAs (C) and in some of the junctions only a small amount of ND-NMBDs are present (D) (Figure1. A to D). The neuromuscular junction is unique for each motor unit, meaning each

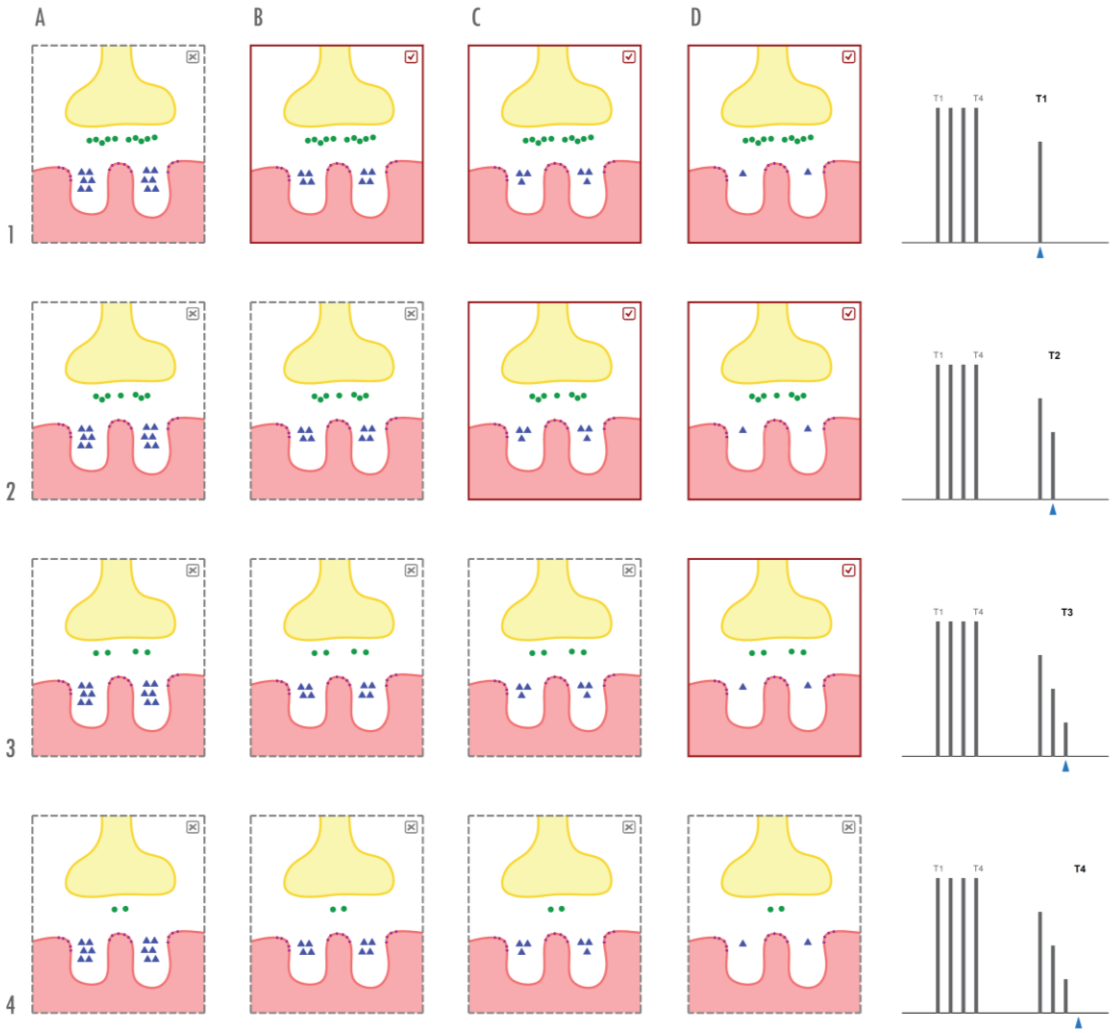

Figure 1. Schematic pattern for Non-depolarizing muscle relaxant agents' interaction within the neuromuscular junction. *A-D* presents different groups of junctions at similar time frames regarding the *drug concentration* within each group of junctions. *1-4* presents those junctions at *different times*, shown by decreased acetylcholine molecule concentration within every junction. Blue triangles represent molecules of Non-depolarizing muscle relaxant agents. Green dots represent acetylcholine molecules.

muscle cell is innervated by only one motor neuron ending. This unit works on an all-or-none basis, meaning a muscle fiber either contracts at its full strength or does not. The different contraction levels in one muscle are secondary to the number of muscle cells contracted at any given time. As the number of contracted muscle cells increases, the whole muscle tone will also increase. The thumb movement during ulnar TOF monitoring follows the same pattern: as the number of contracting muscle cells decreases, the thumb moves less.

Hypothetically, during the first impulse of TOF, about 1,000,000 molecules of Ach will be released to all the types mentioned above of junctions (A to D). Ach molecules cannot overcome the competition in the type A junction since there are plenty of ND-NMBA molecules in the junction. Thus, the outcome will be absent mechanical muscle response in the type A junction. At the same time, in the other three types of junctions (B, C, and D), the winner of the competition between Ach and ND-NMBAs would be Ach because of its larger quantity in comparison to ND-NMBAs,

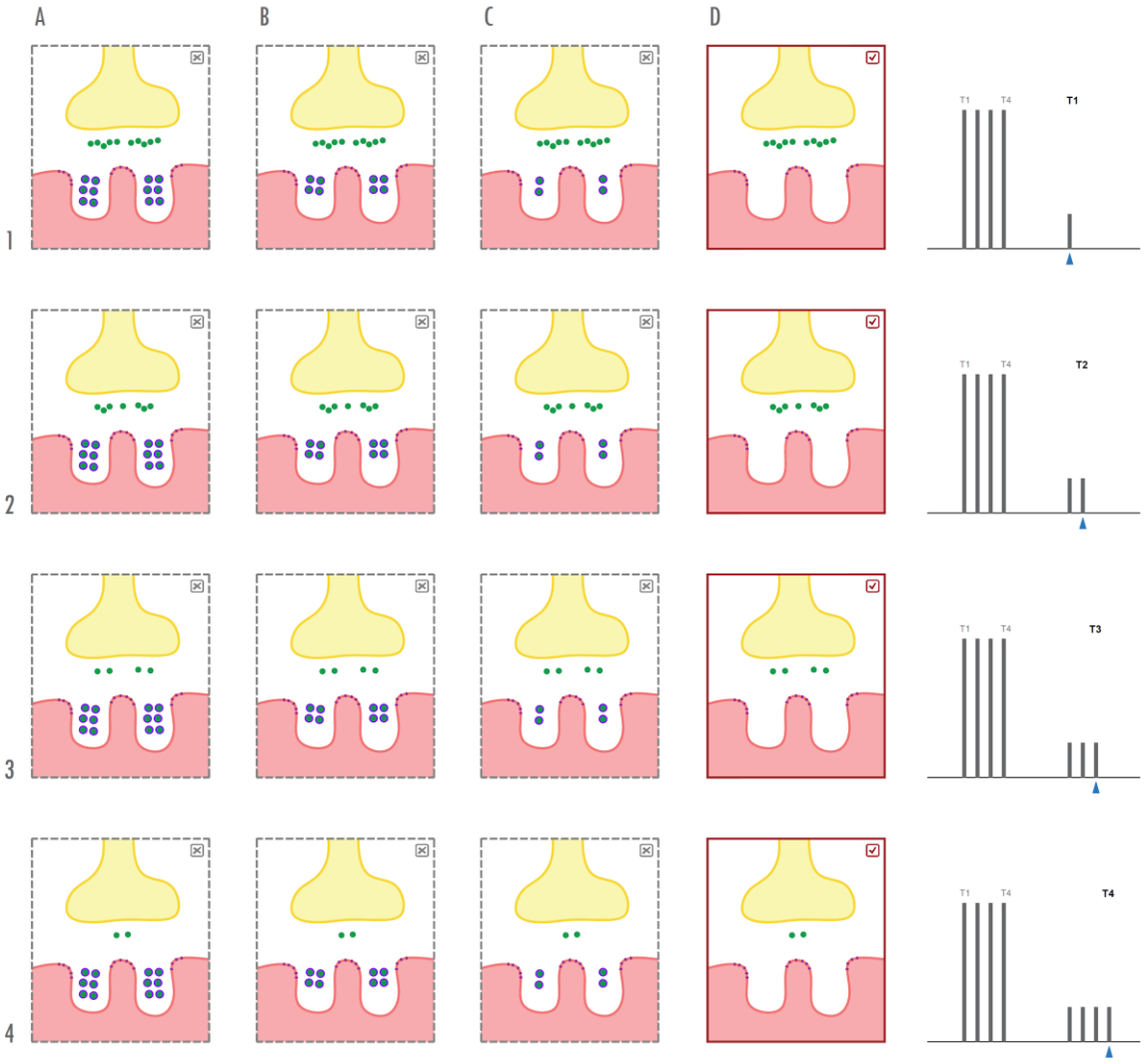

Figure 2. Schematic pattern for depolarizing muscle relaxant agents' interaction within the neuromuscular junction. *A-D* presents different groups of junctions at similar time frames regarding the *drug concentration* within each group of junctions. *1-4* presents those junctions at *different times*, shown by decreased acetylcholine molecule concentration within every junction. Large Blu dots represent molecules of depolarizing muscle relaxant agents. Green dots represent acetylcholine molecules.

which will cause muscle contraction in type B, C, and D junctions. Thus, the outcome of the first electrical impulse would be a mechanical response in ¾ of muscle cells and a response with 75% height of the graph compared to a non-relaxed patient (Figure 1, first row).

The second immediate impulse will release fewer Ach molecules. Contrary to the first impulse, the amount of Ach after the second impulse is insufficient to elicit contraction in type B. Therefore, they remain relaxed like type A junction. However, this amount of Ach is enough for type C and D junctions to respond, and we will see a mechanical response in 2/4 or half of muscle units with a 50% decrease in graph height compared to non-relaxed status (Figure 1, second row).

The same scenario applies to the third and the fourth impulses, which would cause ¼ 0r 25% and 0/4 or 0% height in TOF due to responsiveness of type C and D junctions, respectively (Figure 1, third and fourth row respectively).

This theory also explains the decreased muscle response and lack of fade after injection of D-NMBAs. As we know, D-NMBAs are agonists to nAchR, just like Ach, meaning that they do not compete for the receptor sites. If D-NMBA blocks the junction, no matter how many D-NMBA molecules are present, Ach cannot play a significant role since there is no competition between them. The junction remains blocked during the first to the fourth impulse and will not respond to any of them. The same thing applies to unblocked junctions; if they are not blocked, they will respond the same to all four impulses, which means every impulse activates the exact number of unblocked junctions and cannot activate the exact number of blocked junctions. The result is a homogenous decreased number of responsive units. Thus, there would be no fade, and all responses' heights are equal but less than those of non-relaxed patients (Figure 2).

We believe this approach of abstracting the mechanism behind the Fade phenomenon is novel. However, like any other physiologic event, this process is much more complex than this, and other mechanisms or interpretations are probable. We hope that this explanation is a guide for further cellular and subcellular studies in the field; however, Ludwig Mies van der Rohe, one of the most influential architects of the 20th century, has emphasized the importance of simplicity and conciseness in his famous phrase: “Less is more.”. As physicians and teachers, we hope our simple explanation will make it easier for other clinicians and learners to remember or apply.

Conclusion

Here, a theoretical explanation for the fading phenomenon is provided based on the heterogeneous distribution of drugs and its probable effects on the feature of TOF monitoring of D-NMBA vs ND-NMBA drugs, in the hope of guiding further studies.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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