Current Anesthesiology Reports (2020) 10:85–89
https://doi.org/10.1007/s40140-020-00392-8

NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Evaluation of the Efficacy and Safety of Neostigmine in Reversing Neuromuscular Blockade

D. Schmartz[1] · P. Bernard[1,2] · R. Sghaier[1,2] · T. Fuchs-Buder[1,2]

Published online: 11 April 2020

Abstract

Purpose of Review The minimum degree of neuromuscular recovery required before extubating the patient has progressively increased from a train-of-four ratio of 0.7 to a train-of-four ratio ≥ 0.9. The aim of the review is to evaluate the efficacy and the safety of neostigmine in antagonizing nondepolarizing neuromuscular block considering the new endpoint.

Recent Findings Increasing evidence suggests limited efficacy of neostigmine when a TOF ratio ≥ 0.9 is considered as appropriate endpoint.

Summary The currently accepted endpoint of adequate neuromuscular recovery challenges the efficacy of neostigmine. At least under volatile anesthesia, neostigmine can no longer be considered as an efficient drug to reverse moderate neuromuscular blockade, but it still allows to accelerate neuromuscular recovery when given at more advanced degrees of spontaneous recovery (i.e., a TOF ratio ≥ 0.4). Moreover, neostigmine-based reversal is associated with a higher incidence of adverse effects compared with sugammadex.

Keywords Neuromuscular blockade · Reversal · Neostigmine · Sugammadex · Residual paralysis · Safety · Adverse events

Introduction

With d-tubocurarine, Griffith and Johnson introduced in 1942 the clinical use of neuromuscular blocking agents (NMBA) in anesthesia practice [1]. Of interest in this context, it was already known at that time that the pharmacodynamic effects of nondepolarizing NMBA could be reversed by cholinesterase inhibitors. However, all 25 surgical patients initially exposed by Griffith and Johnson to curare recovered spontaneously without the need of a reversal agent. Moreover, in the first large cohort reporting the use of curare, more than 1000 patients received d-tubocurarine and no clinical signs of residual paralysis were observed in any of these patients [2]. Hence, just in two patients in this series, a cholinesterase inhibitor was administered. This changed fundamentally when Beecher and Todd reported in 1954 a 35 times increase in death after (relaxant anesthesia) compared with a relaxant-free technique [3]. Important in this context, the fatal outcome was also observed in otherwise healthy patients. It could best be explained with persistent residual paralysis contributing to respiratory failure. Accordingly, to this observation, the strategies to manage recovery from neuromuscular blockade changed, proposing now that it is safer to always use neostigmine when nondepolarizing relaxants have been administered [4]. However, in the following, the adherence to this concept changed considerably, and routine reversal becomes rather infrequent [5–7]. As shown in a recent survey, less than 20% of European anesthesiologists and around 35% respondents from the USA administered routinely a cholinesterase inhibitor when a nondepolarizing neuromuscular blocking drug was used [7]. Surprisingly, in the perception of many anesthesiologists, the side effects of cholinesterase inhibitors are more harmful to patients than the clinical consequences of residual

This article is part of the Topical Collection on *Neuromuscular Blockade*

✉ T. Fuchs-Buder
t.fuchs-buder@chru-nancy.fr

D. Schmartz
denis.schmartz@chu-brugmann.be

P. Bernard
paul_bernard@me.com

R. Sghaier
raouf.sghaier@icloud.com

[1] Department of Anaesthesiology, Université Libre de Bruxelles, Brussels, Belgium

[2] CHRU Nancy, Nancy, France

paralysis [8]. Thus, despite good evidence that monitoring and pharmacological reversal are effective key elements to avoid postoperative residual paralysis and to improve patient's outcome, most anesthesiologists still do neither monitor nor reverse depolarizing neuromuscular block [9, 10].

Nondepolarizing neuromuscular blocking agents such as rocuronium or cisatracurium bind to post-junctional nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction to inhibit neuromuscular transmission. This binding to nAChR is competitive. As a consequence, increasing the concentration of nondepolarizing NMBA will increase the depth of neuromuscular blockade, and on the other hand, increasing the concentration of acetylcholine will facilitate neuromuscular transmission [11]. Thus, in clinical practice, reversal of neuromuscular blockade can be achieved by two different mechanisms:

- A direct decrease in the concentration of the neuromuscular blocking agent at the nAChR (i.e., (cleaning) the nAChR). This is the mechanism of action of sugammadex, which directly encapsulates steroidal neuromuscular blocking agents.
- A decrease in the enzymatic metabolism of acetylcholine and thus in increase in acetylcholine which competes with the nondepolarizing neuromuscular blocking agent for the postsynaptic nAChR, thus diminishing the effect of the NMBA and facilitating neuromuscular recovery. This indirect way to reverse neuromuscular block corresponds to the mechanism of action of cholinesterase inhibitors.

Three cholinesterase inhibitors are available for clinical use: neostigmine, edrophonium (not available to antagonize neuromuscular block in some countries), and pyridostigmine. Neostigmine is by far the most frequently used of them. In the following section, the efficacy and safety of neostigmine in antagonizing nondepolarizing neuromuscular blockade is reviewed.

Efficacy

Because of its above described indirect mechanism of action cholinesterase, inhibitors reverse all competitive binding neuromuscular blocking agents and thus, all nondepolarizing NMBA. However, it may also explain the following limitations of neostigmine:

- Indeed, a certain degree of spontaneous recovery is required before neostigmine can efficaciously displace the nondepolarizing NMBA from its binding to the postsynaptic nAChR [12].
- Moreover, acetylcholinesterase is present throughout the parasympathetic nervous system, and thus, the effect of neostigmine is not limited to the neuromuscular junction. Muscarinic side effects occur at the cardiac, alimentary, and respiratory system leading to bradycardia, increased salivation, bowel motility, nausea, vomiting, and bronchoconstriction. They can be attenuated by the concomitant administration of anticholinergic drugs like atropine and glycopyrrolate [13].
- Once the acetylcholinesterase completely inhibited any further increase in the dose of neostigmine will not further increase its efficacy to reverse neuromuscular block [13]. For neostigmine this ceiling effect is reached at doses of 60–70 μg/kg, thus within the clinically relevant range.

Efficacy of Neostigmine-Based Reversal: Theoretical Considerations

The efficacy of neostigmine to prevent residual paralysis depends on the following factors:

a) The pre-reversal degree of spontaneous recovery
b) The dose of neostigmine
c) The reversal interval (i.e., time interval between injection of neostigmine and recovery to the defined endpoint)
d) The definition of an acceptable degree of neuromuscular recovery

Of interest in this context, the benchmark for adequate neuromuscular recovery has been revised serval times over the last decades [14–17]. Initially, a train-of-four ratio ≥ 0.7 was considered as an adequate level of neuromuscular recovery [14]. This was based on the observations on forced vital capacity and maximum inspiratory force at different degrees of residual paralysis. However, improving the understanding of pathophysiologic consequences of residual paralysis led to a reconsideration of this benchmark, which in the following suggestively increased to a TOF ratio of 0.8 and 0.9. Indeed, at a TOF ratio < 0.9 hypoxic respiratory control, coordination of the laryngeal muscles, and the integrity of the upper airway are still affected and are leading to an impaired ability to swallow and to protect the upper airway [15–17]. Thus, even those relatively small degrees of residual paralysis must be reliably treated before extubating the patient to prevent harm. Finally, the threshold depends also on the measurement method. In clinical practice, acceleromyography (AMG) is most often used to assess quantitatively the degree of neuromuscular blockade, and compared with the reference method, i.e., mechanomyography, AMG overestimates the degree of neuromuscular recovery; average baseline TOF ratios are typically 1.15. Hence, when AMG is used, the benchmark for adequate neuromuscular recovery further increases to unity [18].

This increased threshold, however, has consequences for the efficacy of neostigmine-based reversal. Indeed,

Kirkegaard et al. observed that increasing the threshold from a TOF ratio of 0.7 to a TOF ratio of 0.9 limited the efficacy of neostigmine. After 70-μg/kg of neostigmine was given at 2/4 TOF responses, it took 7.6 min to reach a TOF ratio of 0.7 and 9.8 min to reach a TOF ratio of 0.8, thus indicating clinically acceptable efficacy. However, it took 20.2 min to reach the threshold of 0.9. According to their finding, it was not possible to recover to a TOF ratio of 0.9 within 30 min in all patients, regardless of the number of TOF responses present before starting neostigmine-based reversal [19]. Similar results were reported by others, too [20]. Hence, while neostigmine has been an efficient drug, as long as the endpoint was ≤ TOF ratio 0.8, it becomes a limited efficacy with an endpoint of ≥ TOF ratio 0.9. These observations may best be explained by neostigmine's the ceiling effect. Indeed, once a 100% inhibition of the enzyme acetylcholine esterase is reached by neostigmine, any further increase in the dose of neostigmine will not further improve its efficacy; the observed ceiling effect led to a plateau. There is evidence in humans that this phenomenon occurs already at neostigmine doses within its clinical range, i.e., 40–70 μg/kg [21]. Thus, increasing the doses of neostigmine above 70 μg/kg will not further increase its efficacy to reach a TOF ratio ≥ 0.9. As a consequence, the only remaining variables that may potentially be modified in clinical practice are the pre-reversal degree of spontaneous recovery and the reversal interval. However, reversal intervals > 15 min are frequently not achieved in the operating room due to production pressure and are associated with an increased risk of premature extubation. This limited therapeutic range is in line with findings from Baurin et al. determining the conditions to optimize the efficacy of neostigmine. They proposed a pre-reversal twitch height of 25% to reach a TOF ratio > 0.9 after a 40-μg/kg neostigmine within 15 min [22]. Administration of neostigmine at lower levels of spontaneous recovery led to incomplete recovery at 15 min, independently of the dose of neostigmine. Of interest in this context, Tajaate et al. recently published a systematic review on neostigmine-based reversal of intermediate acting neuromuscular blocking agents to prevent postoperative residual paralysis [23••]. When neostigmine was given at moderate levels of residual block (i.e., spontaneous pre-reversal T1 between 10% and 25% of baseline), the mean reversal time was around 11 min. However, they found evidence for a significant difference between total intravenous anesthesia background and volatile anesthesia background. Mean reversal time was 8 min and 21 min, respectively ($p < 0.0001$). Thus, especially when given during volatile anesthesia, the efficacy of neostigmine seems to be significantly reduced. With regard to the required pre-reversal degree of spontaneous recovery, it is generally recommended to wait until all for responses of the TOF stimulation are visible before giving 40-μg/kg neostigmine [24]. Moreover, in patients with more advanced spontaneous recovery and thus smaller degrees of residual paralysis, a smaller dose of neostigmine (20–30 μg/kg) led to adequate reversal within 10 min [25, 26].

Efficacy of Neostigmine-Based Reversal: Practical Observations

In the following, the efficacy of neostigmine in reversing nondepolarizing neuromuscular blockade will be evaluated in clinical practice.

Surprisingly in this context, Fortier et al. presented in 2015 the RECITE study, a Canadian prospective multicenter study on the incidence and severity of residual neuromuscular blockade and they found no difference in the incidence of residual paralysis whether patients received neostigmine or not [27]. According to their results, the overall incidence of residual paralysis, defined as a normalized TOF ratio < 0.9, was 63.5%. It was 64.6% in patients being reversed with neostigmine and it was 60.3% in those patients not receiving the drug. The authors concluded that neostigmine may not have significantly reduced the incidence of residual paralysis. These results were recently confirmed by the US-RECITE study. They reported an incidence of residual paralysis defined as a TOF ratio < 0.9 of 65% despite the use of neostigmine and a peripheral nerve stimulator [28•]. Several studies confirmed that the limited efficacy of neostigmine to reduce residual paralysis in current clinical practice has been confirmed by several other studies. These astonishing findings had been explained by poor adherence of the practicians to the existing recommendations for the use of neostigmine, i.e., proper timing and dosing of neostigmine administration.

Hence, Thilen et al. evaluated whether a guideline based of best available evidence about neuromuscular management could contribute to improve the efficacy of neostigmine to treat residual paralysis [29••]. Dosing and timing of neostigmine was standardized according to the findings in the literature as follows: 40-μg/kg neostigmine should be given only when all four responses after TOF stimulation were again visually detectable and at least a 10 min interval between administration of neostigmine and extubation had to be respected. Despite good adherence to this strict protocol, the incidence of residual paralysis remained unacceptably high. While the incidence of massive residual paralysis, defined as a TOF ratio ≤ 0.7, could be eliminated with this protocol, the incidence of shallow (but still clinically relevant) postoperative residual neuromuscular blockade (TOF ratio < 0.7 and ≤ 0.9) remains elevated with an incidence of 35% for patients managed according to the protocol. Thus, even with this, a (best-case scenario) 35% of patients still had persistent residual paralysis after neostigmine-based reversal.

Increasing evidence suggests that with a TOF ratio > 0.9 (or 1.0 when assessed by acceleromyography) as endpoint, neostigmine is of limited efficacy to reverse moderate levels of neuromuscular block. However, it is still clinically useful to accelerate recovery from shallow neuromuscular blockade (i.e., a TOF ratio > 0.4). Indeed, neostigmine doses on 20–35 μg/kg are sufficient to reverse shallow neuromuscular blockade within a 10-min interval [25, 26].

Safety of Neostigmine-Based Reversal

- In order to attenuate the muscarinic side effects of neostigmine s.a. bronchoconstriction or bradycardia, an anticholinergic drug like glycopyrrolate should be given with neostigmine.
- When given in absence of neuromuscular blockade, neostigmine itself may have neuromuscular blocking properties; thus, leading to a reduction of the TOF ratio rather than accelerating its recovery. This may impair upper airway and breathing function leading finally to adverse postoperative respiratory events [30–32]. However, the clinical consequence of this phenomenon was not fully understood. Of interest in this context are findings from Murphy et al. In a conclusive clinical study y-they could show thatOf interest in this context are findings from Murphy et al. In a conclusive clinical study y-they could show that administration of 40-μg/kg neostigmine at neuromuscular recovery (TOF rain ≥ 0.9) was not associated with any clinical evidence of reappearance of muscle weakness [33••]. Thus, at least at these clinically relevant doses, neostigmine seems not to have any paradoxical effects. These findings further encourage routine reveal of depolarizing neuromuscular blockade.
- Of interest in this context, the efficacy and safety of neostigmine-based reversal and sugammadex-based reversal was recently compared in a meta-analysis by Hristovska et al. [34••]. Unsurprisingly, sugammadex reverses neuromuscular blockade more rapidly than neostigmine. However, it was also associated with significantly fewer adverse events. They observed significantly fewer composite adverse events in patients antagonized with sugammadex compared with neostigmine, with a number needed-to-treat (NNT) of 8. Moreover, they confirmed previous studies reporting an increased risk of postoperative nausea and vomiting as well as a higher risk for bradycardia and postoperative residual paralysis after neostigmine-based reversal when compared with sugammadex. Thus, sugammadex reverses neuromuscular blockade faster than neostigmine regardless of its depth and is associated with fewer adverse effects.

Conclusion

The currently accepted endpoint of adequate neuromuscular recovery of TOF ratio 0.9 or even 1.0 challenges the efficacy of neostigmine. Because of the ceiling effect of neostigmine, increasing its dose over 70 μg/kg will not further increase its efficacy. Moreover, an interval between injection of neostigmine and recovery to the defined endpoint over 10–15 min is poorly accepted in clinical practice. As a consequence, the pre-reversal degree of spontaneous recovery is the only variable allowed to compensate for the increased endpoint. At least under volatile anesthesia, neostigmine can no longer be considered as an efficient drug to reverse moderate neuromuscular blockade (i.e., TOF count around 4), but it still allows to accelerate neuromuscular recovery when given at more advanced degrees of spontaneous recovery (i.e., a TOF ratio ≥ 0.4). Moreover, neostigmine-based reversal is associated with a higher incidence of adverse effects compared with sugammadex.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Griffith HR, Johnson GE. The use of curare in general anesthesia. Anesthesiology. 1942;3:418–22.
2. Gray TC, Halton J. A milestone in anaesthesia? (d-Tubocurarine chloride). Proc Roy Soc Med. 1946;34:400–10.
3. Beecher HK, Todd DP. A study of deaths associated with anesthesia and surgery. Ann Surg. 1954;140:2–34.
4. Gray TC, Wilson F. The development and use of muscle relaxants in the United Kingdom. Anesthesiology. 1959;20:519–29.
5. Fuchs-Buder T, Hofmockel R, Geldner G, Diefenbach C, Ulm K, Blobner M. The use of neuromuscular monitoring in Germany. Anaesthesist. 2003;52:522–6.
6. Duvaldestin P, Cunin P, Plaud B, Maison P. French survey of neuromuscular relaxant use in anesthetic practice in adults. Ann Fr Anesth Reanim. 2008;27:483–9.
7. Osmer C, Vogele C, Zickmann B, Hempelmann G. Comparative use of muscle relaxants and their reversal in three European countries: a survey in France, Germany and Great Britain. Eur J Anaesthesiol. 1996;13:389–99.
8. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopeze A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg. 2010;111:110–9.
9. Tramèr MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. Br J Anaesth. 1999;82:379–86.
10. Baillard C, Clec'h C, Catineau J, et al. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth. 2005;95:622–6.

11. Naguib M, Flood P, McArdle JJ, Brenner HR. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. Anesthesiology. 2002;96:202–31.
12. Goldhill DR, Carter JA, Suresh D, Whitehead JP, Flynn PJ. Antagonism of atracurium with neostigmine. Effect of dose on speed of recovery. Anaesthesia. 1991;46:496–9.
13. Lorrain PE, Schmartz D, Fuchs-Buder T. Neostigmine: mechanism of action, dosing, and factors determining adequacy of recovery following administration. Curr Anethesiol Rep. 2018;8:145–9.
14. Ali HH, Utting JE, Gray TC. Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth. 1970;42:967–78.
15. Eriksson LI. Reduced hypoxic chemosensitivity in partially paralyzed men. A new property of muscles relaxants? Acta Anaesthesiol Scand. 1996;40:520–3.
16. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology. 1997;87:1035–43.
17. Eikerman M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. Am J Respir Crit Care Med. 2007;175:9–15.
18. Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. Anesthesiology. 2004;100:1119–24.
19. Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. Anesthesiology. 2002;96:45–50.
20. Kopman AF, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? Anesth Analg. 2004;98:102–6.
21. Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Severinsen I, Bülow K. Time to peak effect of neostigmine at antagonism of atracurium- or vecuronium-induced neuromuscular block. J Clin Anesth. 1995;7:635–9.
22. Baurin MJ, Dernovoi BS, D'Hollander AA, et al. Conditions to optimise the reversal action of neostigmine upon vecuronium-induced neuromuscular block. Acta Anaesthesiol Scand. 1996;40:574–8.
23.•• Tajaate N, Schreiber JU, Fuchs-Buder T, Jelting Y, Kranke P. Neostigmine-based reversal of intermediate acting neuromuscular blocking agents to prevent postoperative residual paralysis. A systematic review. Eur J Anaesthesiol. 2018;35:184–92 **New insights about the time interval needed after neostigmine to antagonize moderate neuromuscular blockade.**
24. Plaud B, Debaene B, Donati, Marty J. Residual paralysis after emergence from anesthesia. Anesthesiology. 2010;112:1013–22.
25. Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. Anesthesiology. 2010;112:34–40.
26. Fuchs-Buder T, Bauman C, De Guis J, Guerci P, Meistelman C. Low-dose neostigmine to antagonise shallow atracurium neuromuscular block during inhalational anesthesia: a randomized controlled trial. Eur J Anaesthesiol. 2013;30:594–8.
27. Fortier LP, McKeen D, Turner K, de Médicis É, Warriner B, Jones PM, et al. The RECITE study: a Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. Anesth Analg. 2015;121:366–72.
28.• Saager L, Maiese EM, Bash LD, et al. Incidence, risk factors, an consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECIUTE-US study. J Clin Anesth. 2019;55:33–41 **The article gives an overview over current practice in neuromuscular management in the US.**
29.•• Thilen SR, Ng IC, Cain KC, Treggiari MM, Bhananker SM. Management of rocuronium neuromuscular block using a protocol for qualitative monitoring and reversal with neostigmine. Br J Anaesth. 2018;121:367–77 **Shows limitations of neostigmine, even when used according to best available practice.**
30. Payen JP, Hughes R, Al Azawi S. Neuromuscular blockade by neostigmine in anesthetized man. Br J Anaesth. 1980;52:574–8.
31. Caldwell JE. Reversal of residual neuromuscular with neostigmine at one of four hours after a single intubating dose of vecuronium. Anesth Analg. 1995;80:1168–74.
32. Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. BMJ. 2012;345:e6329.
33.•• Murphy GS, Szokol JW, Avram MJ, et al. Neostigmine administration after spontaneous recovery to a train-of-four ratio of 0.9 to 1.0. Anesthesiology. 2018;128:27–37 **Clinical relevant information about the paradoxical effect of neostigmine.**
34.•• Hristovska AM, Duch P, Allingstrup M, Afshari A. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2018;73:631–41 **Compares efficacy and safety of neostigmine-based reversal with sugammadex-based reversal.**