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EDUCATIONAL SERIES

Managing residual neuromuscular blockade in NZ

About the Reviewer

Dr John Barnard

Dr John Barnard works as an anaesthetist at Waikato Hospital with a part time academic component. In addition to his role in the operating theatres, four years ago he became the Clinical Director of the Hospital Pharmacy and Chairman of the hospital's Medicines and Therapeutics Committee. The combination of these roles placed him in an interesting position with the introduction of sugammadex to the New Zealand market and the creation of our national Hospital Medicines List. He took an active part in lobbying Pharmac to open up the planned highly restricted application of sugammadex to the unexpected difficult airway/failed intubation scenario. Thankfully Pharmac responded and the profession in NZ now has reasonable access to this new class of reversal agent. One of the spin off effects of this access is the opportunity to re-examine the entire management of neuromuscular blockade and the physiology of the neuromuscular junction.

Introduction

This review is intended as an educational resource for health professionals. It discusses the incidence and management of residual neuromuscular blockade. Peer-reviewed clinical trial evidence is presented with accompanying expert commentary that is intended to inform readers about advancing clinical practice in this area.

The issue of residual neuromuscular blockade?

The introduction of curare to anaesthesia in the 1940s was associated with an almost 6-fold increase in anaesthetic mortality.[1] Subsequently, techniques for monitoring and managing neuromuscular blockade greatly improved patient safety and the use of synthetic neuromuscular blocking agents (NMBAs) during anaesthesia became one of the most important advances in anaesthesiology.[2] Unfortunately, the residual effects of NMBAs may persist into the early postoperative recovery period, impairing airway protective reflexes, adversely affecting respiratory function, producing muscle weakness, and ultimately prolonging time spent in the post-anaesthesia care unit (PACU).[3-8]

The challenge is how best to combine muscular relaxation throughout the operative procedure without exposing patients to the risk of residual neuromuscular blockade.[9] This challenge is compounded by differences in the duration of action of different NMBAs, the desired depth of neuromuscular blockade, variability in patient populations and interactions with other drugs.[10] There is recent evidence that deep neuromuscular blockade significantly improves surgical field conditions in a range of surgeries including laparoscopic surgery, and there is an increasing requirement for deep block.[11-13] While the risk of residual neuromuscular blockade appears to be related to the duration of action of the NMBA, a number of recent studies have shown high rates of this complication even with the use of shorter-acting agents.[4]

Defining adequate recovery from neuromuscular blockade

Residual neuromuscular blockade (also termed postoperative residual curarisation [PORC]) is commonly measured using a train-of-four (TOF) stimulator.[14] Comparison of the fourth and first twitches of the TOF gives rise to the TOF ratio.[15] In the control situation (before administration of a muscle relaxant) the muscle twitches have the same amplitude and the TOF ratio is ≥1.[16] At a TOF ratio of 0.4 the patient is generally unable to lift their arm or head and vital capacity and inspiratory force is reduced, at 0.6 they are able to lift their head and protrude their tongue, at 0.75 a valid cough reflex is present and at 0.9 complete recovery of lung function is evident; however, there is much interpatient variability in these clinical signs.[16,17]

Until the early 1990s, a TOF ratio ≥0.7 was considered an indication of adequate reversal of paralysis.[18] More recent findings from volunteer and clinical studies have shown that residual neuromuscular blockade may be present at a TOF ratio up to 0.9 and that such block is associated with significant adverse effects.[5-8,19-28] A number of studies in young healthy volunteers, in the absence of other anaesthetic agents, have demonstrated that minimal levels of residual blockade (TOF ratio of 0.70 to 0.9) have significant effects on pharyngeal, respiratory and skeletal muscle function (see Table).[20-25] Of particular note, an impaired hypoxic ventilator drive has been observed in studies examining the effect of vecuronium in awake volunteers.[23,24] In these studies, the ventilator response to hypoxia was significantly reduced at a TOF ratio of 0.7; however, the response to hypercapnoea was maintained.

Studies have shown that residual neuromuscular blockade may result in delays in extubation, muscle weakness, aspiration pneumonia; hypoxaemia, visual disturbance, difficulty sitting and speaking during early recovery, delays in discharge from the PACU, the need for prolonged antibiotic therapy and increased financial costs (see Table).[5,6,8,17,26-29]

An open-label prospective randomised cohort study investigating pulmonary function in the immediate postoperative period in 150 patients who had received either vecuronium, atracurium or rocuronium and reversal of neuromuscular blockade found that residual neuromuscular blockade (TOF ratio <0.9) resulted in reductions in forced vital capacity and peak expiratory flow.[7] And a study by Berg et al. revealed a 3.5-fold higher risk of postoperative pulmonary complications in those with, versus those without, residual neuromuscular blockade (TOF ratio <0.7) in the PACU after receiving pancuronium.[8] In a small number of cases such symptoms are clinically relevant as they have the potential to lead to severe permanent brain damage or death.[17]

Table: A number of studies have demonstrated a variety of concerning clinical symptoms associated with residual neuromuscular blockade

Volunteer studies[20-25]	Clinical studies in surgical patients[26,27]
Impaired pharyngeal function	Delays in meeting PACU discharge criteria and achieving actual discharge
Increased risk of aspiration	Symptoms and signs of profound muscle weakness
Upper airway obstruction	Increased risk of postoperative hypoxaemia
Impaired hypoxic ventilator drive	Prolonged postoperative intubation times (cardiac surgical patients)
Profound symptoms of muscle weakness	Increased risk of postoperative respiratory complications

It is now widely accepted that a TOF ratio <0.9 defines incomplete neuromuscular recovery.[4] The new gold standard for acceptable postoperative recovery is a TOF ratio ≥0.9 and ideally this ratio should be achieved before tracheal extubation.[4,15]

What is the incidence of residual neuromuscular blockade?

A number of studies have demonstrated an alarmingly high incidence (4-88%) of residual paresis in the PACU; pancuronium tended to be associated with higher rates in a number of these studies, and this agent is rarely used in current practice.[4,26,30-33] The frequency of this phenomenon depends on the diagnostic criteria, the type of NMBA used, whether a reversal agent is used and whether neuromuscular monitoring is undertaken.[17] A meta-analysis looking at data from 24 clinical trials involving over 3300 patients found residual blockade (TOF ratio <0.9) in 41% of those receiving intermediate-acting muscle relaxants.[34] In line with these findings, a recent prospective observational study involving 102 patients at a New Zealand tertiary hospital, most of whom had received an intermediate-acting muscle relaxant, found a 31% incidence of residual neuromuscular blockade (TOF ratio <0.9) in the PACU.[35] Furthermore, among those with residual neuromuscular blockade, the mean interval between last dose of muscle relaxant and arrival in the PACU was 81 minutes, emphasising the fact that even after an hour has past post NMBA dose, there is still a risk of residual paralysis.

In a study by Hayes and colleagues, among 150 patients arriving in the PACU after receiving an intermediate-acting NMBA (vecuronium, atracurium or rocuronium), 64%, 52% and 39%, respectively, exhibited residual blockade (defined as a TOF ratio <0.8; this value was derived from recommendations at the time suggesting that a TOF ≥0.8 was necessary to ensure safety in the postoperative period).[30] This study reported that a similar percentage of patients were not able to maintain a 5 second leg or head lift, and did not attain a TOF ratio ≥0.8 until a mean of 9.2 min (vecuronium), 6.9 min (atracurium) and 14.7 min (rocuronium) after arrival on the recovery ward. Of note, 68% of patients in the study had undergone reversal of neuromuscular blockade and there was no significant difference in the incidence of postoperative residual blockade in those receiving or not receiving a reversal agent; none of these patients had been monitored for neuromuscular function.[30]

The importance of monitoring

The problem of residual neuromuscular blockade is under-recognised and its implications appear to be underappreciated.[17,36] Studies in New Zealand and overseas suggest that a considerable number of clinicians do not consider residual neuromuscular blockade to be an important safety issue.[25,36] It is therefore not surprising that only small numbers monitor neuromuscular function in the operating room. In fact, a recent meta-analysis has revealed that large numbers of practitioners choose not to monitor intraoperative neuromuscular function, and fail to administer reversal agents when appropriate.[34]

A survey undertaken in New Zealand and Australia in 2011 investigated the attitudes and practices of 678 anaesthetists in relation to their management of neuromuscular blockade monitoring.[36] While 70% of respondents believed routine monitoring would reduce the incidence of residual neuromuscular blockade, only 17% undertook objective monitoring of neuromuscular function. Only 25% were aware that quantitative TOF ratios ≥0.9 were accepted criteria for safe extubation; 52% used clinical judgement only and in 42% of the hospitals in which the respondents practiced, quantitative neuromuscular monitoring was not available. There is a definite need for evidence-based guidelines for the management of neuromuscular blockade in New Zealand and Australia.

Emphasising the inaccuracy of clinical monitoring, one study revealed residual paresis (TOF ratio <0.7) in 58% of patients deemed by anaesthesia care providers to be clinically recovered; these providers assessed patients using the 5 second head lift or hand grip.[37] This clinical measure is unreliable and has been shown to be achievable by some patients with TOF ratios as low as 0.25-0.4.[37] Heier et al. compared clinical signs with TOF measurements at the adductor pollicis and confirmed the inaccuracy of clinical tests.[38]

The good news is that postoperative residual blockade appears to be largely preventable with adequate monitoring and appropriate reversal. A French group demonstrated this after discovering they had a 40% incidence of residual neuromuscular blockade (TOF ratio <0.7).[31] Their subsequent introduction of nerve monitoring and promotion of the use of neostigmine led to a decrease in the incidence of such block (TOF ratio <0.9) to 3% within 8 years.[39]

Factors contributing to residual neuromuscular blockade

The cause of postoperative residual paralysis is multifactorial, but the most common causes are the administration of large doses of NMBAs, attempting to reverse the block too early and the absence of neuromuscular monitoring.[39,40] Some of the other contributing factors are short duration of surgery, older age, higher body mass index, female gender, organ dysfunction, other drugs (including volatile anaesthetics which potentiate neuromuscular blockade and hypothermia).[40-42] Furthermore, certain disease states and medical conditions (particularly myasthenia gravis), electrolyte disturbances and acidosis may potentiate the effect of NMBAs.[43]

While the incidence of residual neuromuscular blockade appears to be higher with long-acting NMBAs such as pancuronium (3-4-fold higher than with intermediate-acting agents), such paralysis is frequently seen with both intermediate- (atracurium, vecuronium, rocuronium and cisatracurium) and short-acting agents (mivacurium).[37,40] Despite the introduction of a number of new NMBAs, such as rocuronium and mivacurium over the last 15 years, there has been no significant observed decrease in the incidence of residual neuromuscular blockade.[44]

Reversing neuromuscular blockade

Conventional reversal of neuromuscular blockade has involved the use of cholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium), administered at reappearance of two twitches of the TOF response, or first signs of clinical recovery.[40] There are a number of disadvantages with using these agents, including the fact that they are only efficacious if recovery is already established, their full effect takes up to 10 minutes to achieve and they have a number of muscarinic side-effects (nausea, vomiting, bradycardia, Q-T prolongation, bronchoconstriction, miosis, stimulation of salivary glands and increased

intestinal tone) requiring the concomitant administration of an antimuscarinic agent.[40] Recent research shows that patients continue to arrive in the PACU with TOF ratios <0.9, despite reversal of intermediate-acting agents.[29]

More recently, sugammadex [Bridion®], a γ-cyclodextrin, which has a high affinity to amino-steroidal NMBAs (particularly rocuronium, to which sugammadex has a 2.5-fold higher affinity than to vecuronium) has been available for the reversal of non-depolarising NMBAs.[40,45] Sugammadex is ineffective against depolarising NMBAs (suxamethonium) and benzylisoquinolinium (atracurium and mivacurium).[40] Sugammadex forms a 1:1 inclusion complex with rocuronium, vecuronium and pancuronium (rocuronium > vecuronium >> pancuronium), thereby terminating their action.[40] If neuromuscular block needs to be re-established after reversal with sugammadex, it is recommended that a benzylisoquinolinium NMBA be used.[40] Sugammadex has demonstrated efficacy in reliably reversing even profound block and may be used for reversal in the situation where the patient `cannot be intubated, cannot be ventilated'.[40,46,47] The agent appears to be well tolerated, and studies are underway to further investigate adverse effects.[40,46]

A recent audit on the use of sugammadex at a single Australian hospital has shown this agent to have a high acceptance rate as an alternative to neostigmine and a significantly lower rate of TOF ratios <0.7 and <0.9 when comparing its use to that of neostigmine or no reversal agent.[48] Sugammadex is able to reverse deeper levels of neuromuscular block than neostigmine in a much shorter timeframe and gives a margin of safety, especially for difficult cases with compromised patients, that has not previously been available.[49] While there is a paucity of data on the pharmacoeconomic aspects of sugammadex use, it is plausible that reduction of postoperative recovery times will increase patient throughput.[50]

In New Zealand, sugammadex is approved for use as a reversal agent for neuromuscular blockade and is listed in Section H of the Pharmac schedule. Use of the agent is restricted to the following situations: 1. Patient requires reversal of profound neuromuscular blockade following rapid sequence induction that has been undertaken using rocuronium (i.e. suxamethonium is contraindicated or undesirable); or 2. Severe neuromuscular degenerative disease where the use of neuromuscular blockade is required; or 3. Patient has an unexpectedly difficult airway that cannot be intubated and requires a rapid reversal of anaesthesia and neuromuscular blockade; or 4. The duration of the patient's surgery is unexpectedly short; or 5. Neostigmine or a neostigmine/anticholinergic combination is contraindicated (for example the patient has ischaemic heart disease, morbid obesity or COPD); or 6. Patient has a partial residual block after conventional reversal.

Economic burden of residual neuromuscular blockade

Residual neuromuscular block increases the risk of complications, especially for those suffering from respiratory comorbidity, increasing the need for additional care.[17] A study at Massachusetts General Hospital has shown that residual neuromuscular block (TOF <0.9) is independently associated with an increased length of PACU stay (on average 80 minutes longer) and that this likely results in subsequent patients having to wait to enter the PACU.[51]

Another aspect is the potential for delayed reversal of muscle relaxation to slow patient turnover in theatre. The economic burden of using a new and relatively expensive drug like sugammadex compared to the established cheap alternative, neostigmine, may be offset by avoiding theatre delays. The Waikato Hospital Anaesthetic Department analysed the first 12 months of sugammadex usage (unpublished data). They noted each time sugammadex was given to facilitate extubation soon after an operation finished, in preference to waiting until neostigmine could be given or would work. These instances were assigned a theoretical time saving of 15 minutes theatre time. Using the then purchase price of $120 and an estimated theatre running cost of $1000/hr, the cost of the time saved by speeding up reversal offset the department's entire expenditure on sugammadex. While this kind of analysis is a gross oversimplification of real theatre dynamics and costs, it highlights the potential for a relatively expensive drug to pay for itself through efficiency gains.

EXPERT COMMENTARY ON KEY STUDIES OF RESIDUAL NEUROMUSCULAR BLOCKADE AND ITS MANAGEMENT

Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study[52]

Authors: Grosse-Sundrup M et al.

Summary: This prospective US cohort study examined the effect on postoperative respiratory complications of an intermediate NMBA during general anaesthesia in 18,579 surgery patients matched with 18,579 reference patients by propensity scores. Use of an intermediate acting NMBA increased the risk of postoperative haemoglobin desaturation <90% after extubation (OR 1.36; 95% CI 1.23-1.51) and the risk of reintubation requiring unplanned admission to ICU (OR 1.40; 95% CI 1.09-1.80). Qualitative monitoring using the TOF ratio did not decrease this risk. Neostigmine reversal increased the risk of both postoperative haemoglobin desaturation <90% (OR 1.32; 95% CI 1.20 -1.46) and reintubation (OR 1.76; 95% CI 1.38-2.26).

Comment: This very large database trawl relies on propensity scoring to adequately remove confounding influences to allow 18,579 patients given an intermediate duration NMBA to be compared to a matched group of 18,579 patients given no relaxant. To my mind the statistically significant differences found provide a strong stimulus to examine the issue using a more rigorous trial design, but they do not conclusively prove that intermediate duration muscle relaxants cause an excess of respiratory complications compared to the non-relaxant general anaesthesia. Looking at the fine print of the propensity scoring, surgical specialty and operation length were used as the matching criteria for operation type. Efforts to ensure the accuracy of this style of matching were not well described and some of the results seem counterintuitive. For instance the factors associated with a need for re-intubation in patients who received an intermediate duration NMBA. Re-intubation was more likely if neostigmine was given versus not given, and if neuromuscular monitoring was used versus clinical assessment of neuromuscular function only.

The flow on discussion about why neostigmine might impair neuromuscular function is interesting and well referenced. This discussion includes reflections on the use of neostigmine in the US (reversal given routinely) versus in Europe (reversal given based on assessment of neuromuscular function). To my mind the single most interesting fact is that neuromuscular monitoring was used in only 50% of the patients receiving NMBAs.

Postoperative residual neuromuscular blockade is associated with impaired clinical recovery[6]

Authors: Murphy GS et al.

Summary: This secondary analysis of data from an RCT (n =149) compared the residual neuromuscular blockade as assessed by a TOF ratio <0.9, with the type, incidence and severity of subjective muscle weakness reported in a PACU. The incidence of muscle weakness symptoms was significantly greater ($p < 0.001$) 20, 40 and 60 minutes after admission in patients with a TOF <0.9 (n = 48) than in those with a TOF ≥0.9 (n = 101). The median number of symptoms observed was also higher from admission (7 vs 2; 99% CI of the difference 4 to 6) to 60 min (2 vs 0; 99% CI of the difference 1 to 2); all $p < 0.0001$.

Comment: This article reports secondary analysis of data from an RCT investigating the value of quantitative monitoring of neuromuscular function using acceleromyography (TOF Watch SX®) versus manual (tactile) TOF monitoring using the same device as a simple nerve stimulator. In this article the data from the original trial was used to retrospectively create two groups of patients based on the measured TOF ratio when the patients first reached the PACU. The unmatched sizes of the two groups of patients reflect the fact that this was secondary analysis. Acceleromyography was used more commonly in the TOF ratio ≥0.9 group (63%) than in the TOF ratio <0.9 group (23%) and the availability of these quantitative values of neuromuscular function will have influenced how the anaesthetists involved managed the neuromuscular blockade. However the defining feature separating the two groups in this study is a robust measurement of neuromuscular function and it would be hard to explain away the results based on some systematic feature of anaesthesia that would not be picked up by the quantified TOF ratio.

Patients were questioned and examined at four time points – on admission to PACU, then 20, 40, and 60 minutes post-admission. A range of questions and tests to demonstrate residual blockade were applied at each time point and most of these had binary outcomes – e.g. the patient did or did not have a symptom, the patient could or could not perform a test. Almost all the patients could complete the study protocol (i.e. they were not markedly sedated). There were highly significant differences between the groups. The rates of related symptoms and signs were also very different. In the TOF ratio <0.9 group 89% found it difficult to perform a 5 second eye opening but only 11% could not perform this test, and in the TOF ratio ≥0.9 group 36% found it difficult and only 1% could not perform this test. The most prevalent positive finding was a subjective feeling of weakness, present in 91% of the more-paralysed group versus 45% in the less-paralysed group. Using a verbal rating scale rather than a binary measure of weakness increased the difference between the two groups. Subjective difficulty with eye opening was probably the best combination of a reasonably sensitive and specific test that was not too demanding on the patient.

Introduction of sugammadex as standard reversal agent: Impact on the incidence of residual neuromuscular blockade and postoperative patient outcome[44]

Authors: Ledowski T et al.

Summary: This prospective audit at a tertiary teaching hospital examined current clinical practice with respect to muscle relaxant reversal and the effect of sugammadex introduction on outcome in 146 patients receiving no reversal, neostigmine or sugammadex. The TOF ratio was <0.7 in 17 patients (9 receiving no reversal, 8 neostigmine) and <0.9 in 47 patients (24 receiving no reversal, 19 neostigmine, 4 sugammadex). Patients receiving sugammadex exhibited fewer postoperative oxygen desaturation episodes (15% vs 33%; $p < 0.05$). Patients with a TOF ratio <0.7 ($p < 0.05$) and <0.9 ($p < 0.01$) were more likely to have x-ray images consistent with postoperative atelectasis or pneumonia.

Comment: This is an appealing work because it is a 'real world' rather than 'research world' study. What happens to the incidence of residual blockade and respiratory complications if the only change you make is to allow free access to sugammadex. Remarkably, even with only 146 patients to work with, the Royal Perth hospital found more than just the predictable lower rates of residual block if sugammadex was the reversal agent. In the PACU they found fewer episodes of desaturation (saturation <96% on 6 L/m O_2) if sugammadex was used. Looking at the subgroup of patients (n = 30) who had a chest x-ray within 30 days of surgery they found higher rates of atelectasis and pneumonic changes in those patients who received no reversal. As in the Gosse-Sundrup paper above, propensity scoring was used to control for the effect of confounding patient and surgery related factors, so this result is open to the same levels of suspicion. Of the 146 patients – 57 received sugammadex, 53 no reversal, 33 neostigmine, and the remaining three I guess did not have the management of reversal documented adequately. Neuromuscular monitoring with nerve stimulation in the operating theatre was used in 129 patients (this seems a very high proportion compared to other centres and could be a measurement effect, i.e. the staff knew the audit was happening or Royal Perth Hospital anaesthetists use neuromuscular monitoring conscientiously) – TOF ratio (clinically assessed) in 79, double burst in 37, and sustained tetanus in 13. As a part-time researcher I would be interested to know how this paper ended up in the Indian Journal of Anaesthesia rather than one of the journals more commonly read by ANZCA specialists. Was the paper rejected by other journals and if it was, what did the editors and reviewers want to see?

Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade[46]

Authors: Abrishami A et al.

Summary: This Cochrane review assessed data from 18 RCTs conducted up to August 2008 on the use of sugammadex for the reversal of neuromuscular blockade induced by steroidal non-depolarising NMBAs and the prevention of residual neuromuscular blockade in 1321 patients undergoing surgery. The analysis suggested that use of sugammadex results in a more rapid reversal of rocuronium-induced neuromuscular blockade than placebo or neostigmine. Optimal dosage is dependent on the depth of block with 2 mg/kg for reversal at T2 reappearance, 4 mg/kg for reversal at 1 to 2 post-tetanic counts, and 16 mg/kg for reversal 3 to 5 min after profound blocks. Sugammadex was also effective in reversing vecuronium or pancuronium-induced neuromuscular blockade; however the number of studies with these agents is very limited. Serious adverse events occurred in <1% of patients and there was no difference in the prevalence of drug-related adverse events between sugammadex and placebo (RR 1.20; 95% CI 0.61-2.37) or sugammadex and neostigmine (RR 0.98; 95% CI 0.48-1.98).
NB. In NZ, sugammadex is not indicated for the reversal of pancuronium-induced neuromuscular blockade.

Comment: This review demonstrated what you would get in 2009 if you selected the evidence using the following criteria - all RCTs on adult patients (≥18 years old) in which sugammadex was compared with placebo or other medications, or in which different doses of sugammadex were compared with each other to be included, all non-randomised trials and studies on healthy volunteers to be excluded. In this case what happened is you found 18 RCTs and a total of only 1321 patients. From these trials sugammadex was more effective and faster acting than neostigmine when the nominated endpoint is achieving a TOF ratio of >0.9. Also there was no difference in the rate of side effects between the two agents. The major reason to highlight this Cochrane review is to demonstrate how limited the conclusions must be if the filter of the evidence is set to 'high quality only'. Like many Cochrane reviews the conclusions reached are solid, however the information is not refined enough to adequately guide clinical decision-making. There will be a lot more data now, but I suspect if the same review was repeated today the conclusions reached would not have changed much. The general requirement to synthesise evidence from sources other than large scale RCTs still applies.

Residual neuromuscular blockade and postoperative pulmonary outcome: The missing piece of the puzzle[53]

Author: Fuchs-Buder T.

Summary/comment: Unfortunately this is a difficult journal to access full text but some relevant articles including this commentary can be found in a recent issue of the European Journal of Anaesthesiology. The commentary provides some insights from six of the articles found in the journal issue. For example the presence of diabetes without any major sequelae increases the duration of action of rocuronium by 30% compared to matched controls and giving dexamethasone 2-3 hours before anaesthesia decreases its duration of action by 20%. The final paragraph is the most telling though, describing the absence of a large RCT addressing the putative link between current practices in reversal of relaxation and postoperative respiratory complications, as "the missing piece of the puzzle".

Does rocuronium-sugammadex reduce myalgia and headache after electroconvulsive therapy in patients with major depression?[54]

Authors: Saricicek V et al.

Summary: This study in 45 patients undergoing electroconvulsive therapy (ECT) compared the development of myalgia and headache after anaesthesia induction with propofol 1 mg/kg intravenously followed by succinylcholine 1 mg/kg (n = 24) or rocuronium 0.3 mg/kg plus sugammadex 4 mg/kg after motor seizure (n = 21). Time to onset of spontaneous respiration and eye opening in response to verbal stimuli were shorter in rocuronium plus sugammadex recipients than in succinylcholine recipients ($p < 0.002$), and myalgia visual analog scale (VAS) scores 2, 6 and 12 hours after ECT and headache VAS scores 2 and 6 hours after ECT were also significantly better in rocuronium plus sugammadex recipients ($p < 0.015$).

Comment: Meanwhile small prospective trials and case series continue to define how the first selective relaxant binding agent is able to provide a new solution to old problems. In this case, if you can't use suxamethonium, what can you use for neuromuscular blockade during ECT that works well and doesn't slow the process down? The combination of a just asleep dose of an IV induction agent, 0.3 mg/kg rocuronium, then 4 mg/kg sugammadex following the convulsion is a useful technique to keep in mind. This technique has the added benefit of reducing myalgia post-procedure.

Concluding remarks/take home messages

There are a number of things we can be reasonably certain about regarding the reversal of neuromuscular blockade.

- Residual neuromuscular blockade in the PACU has not gone away with the change from long duration to intermediate duration neuromuscular blocking drugs
- Clinical assessment of recovery from neuromuscular blockade will not detect minor degrees of residual neuromuscular blockade
- Non-quantitative monitoring of neuromuscular function using nerve stimulation in the operating theatre is nowhere near universal and quantitative monitoring is used even less often
- When reversing the action of vecuronium or rocuronium, sugammadex is both more effective and faster than neostigmine
- We do not adequately understand the negative impact of minor degrees of neuromuscular blockade and we do not adequately understand the side effect profiles of either traditional reversal or reversal with sugammadex.

Over the last 70 years the anaesthetic profession has become quite adept at managing relaxation and reversal. In the coming few years we are unlikely to see the kind of improvement seen when the dangers of partial curarisation were first recognised and neostigmine was first used to reverse the effects of tubocurarine. However, there is clearly room to improve. Normally anaesthetists are swift to seize an opportunity to improve the quality of care and especially to make the process of anaesthesia safer. It is curious then that quantitative monitoring of neuromuscular function is not more routine.

Despite knowing that minor degrees of curarisation in healthy volunteers cause a range of unpleasant and unsafe effects, and that we can't detect this level of residual blockade without quantitative monitoring, we resist investing in this technology. We are apparently comfortable with some proportion of our patients being slightly paralysed for a period of time after surgery. Unless the department you work in makes a special effort to use neuromuscular monitoring well, this proportion is likely to be around 30% of the patients given muscle relaxants. Similarly we are apparently comfortable with administering neostigmine and an anticholinergic agent to a proportion of patients who do not need these medicines, a recipe for net harm rather than net benefit.

Concurrently we have the option to use sugammadex for reversal in place of neostigmine. Is it just cost and a lingering concern about incidence of allergy that has prevented sugammadex becoming the preferred reversal agent? In New Zealand at least there are restrictions in place limiting sugammadex to scenarios where neostigmine wouldn't work (block too deep) or where there

is a particular clinical concern around the use of neostigmine or an anticholinergic medicine (allergies and co-morbidities), so for the moment there is a legislated requirement to use neostigmine in most cases.

To quote Fuchs-Buder[53] the missing piece in the puzzle is a good quality large RCT with hard outcome data comparing sugammadex to neostigmine in a population of interest. Quite possibly it is too late to do this trial in Australia. The results of available research examining the impact of residual curarisation (prospective before and after style trials like Ledowski's[44], retrospective analyses like Grosse-Sundrup's[52], small scale RCTs like Murphy's[6,26] all looking at surgical patient populations, and the various works by Eriksson[21,23,24] and Kopman[25] using well volunteers) may make an ethics committee shy away from allowing a high-risk group of patients to be randomised to neostigmine. From a scientific perspective, not creating the missing piece of the puzzle would be an important opportunity gone begging. In addition, this missing piece has important implications for quality of care and cost effectiveness.

REFERENCES

1. Beecher HK and Todd DP. A study of the deaths associated with anesthesia and surgery: based on a study of 599,548 anesthesias in ten institutions 1948-1952, inclusive. Ann Surg. 1954;140(1):2-35
2. Churchill-Davidson HC and Richardson AT. Decamethonium iodide (C 10): Some observations on its action using electromyography. Proc R Soc Med. 1952;45(4):179-86
3. Bevan DR. Recovery from neuromuscular block and its assessment. Anesth Analg. 2000;90:S7-S13
4. Murphy GS. Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period. Minerva Anesthesiol. 2006;72(3):97-109
5. Kiekkas P et al. Residual neuromuscular blockade and postoperative critical respiratory events: literature review. J Clin Nurs. 2014;Jan 27 [Epub ahead of print]
6. Murphy GS et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. Anesth Analg. 2013;117(1):133-41
7. Kumar GV et al. Residual neuromuscular blockade affects postoperative pulmonary function. Anesthesiology 2012;117(6):1234-44
8. Berg H et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand. 1997;41(9):1095-1103
9. Plaud B. Neuromuscular monitoring, residual blockade, and reversal: time for re-evaluation of our clinical practice. Can J Anaesth. 2013;60(7):634-40
10. Bhaskar SB. Emergence from anaesthesia: Have we got it all smoothened out? Indian J Anaesth. 2013;57(1):1-3
11. Dubois PE et al. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: A randomised controlled trial. Eur J Anaesthesiol. 2014;31(8):430-6
12. Boon M et al. Effect of variations in depth of neuromuscular blockade on rating of surgical conditions by surgeon and anesthesiologist in patients undergoing laparoscopic renal or prostatic surgery (BLISS trial): study protocol for a randomized controlled trial. Trials 2013;14:63
13. Martini CH et al. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. Br J Anesth. 2014;112(3):498-505
14. Ali HH et al. Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth. 1970;42:967-78
15. McGrath CD and Hunter JM. Monitoring of neuromuscular block. Continuing Education in Anaesthesia, Critical Care & Pain. 2006;6:7-12
16. Miller RD. Miller's Anaesthesia. 7th Edition, 2009. Churchill Livingstone
17. Gastagnoli A et al. Post-operative residual curarization (PORC): A big issue for patients' safety, risk management for the future – theory and cases, Dr Jan Emblemsvåg (Ed), ISBN:978-953-51-0571-8 InTech, Available from: http://cdn.intechopen.com/pdfs-wm/36101.pdf (Accessed July 2014)
18. Ali HH et al. The effect of tubocurarine on indirectly elicited train-of-four responses and respiratory measurements in humans. Br J Anaesth.1975;47:570-74
19. Viby-Mogensen J et al. Residual curarization in the recovery room. Anesthesiology 1979;50(6): 539-41
20. Sundman E et al. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: pharyngeal videoradiography and simultaneous manometry after atracurium. Anesthesiology 2000;92(4):977-84
21. Eriksson LI 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(5):1035-43
22. Eikermann M et al. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. Anesthesiology 2003;98(6):1333-7
23. Eriksson LI et al. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 1993;78(4):693-9
24. Eriksson LI et al. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. Acta Anaesthesiol Scand. 1992;36(7):710-5
25. Kopman AF et al. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997;86(4):765-71
26. Murphy GS et al. Post anaesthesia care unit recovery times and neuromuscular blocking drugs: A prospective study of orthopedical surgical patients randomized to receive pancuronium or rocuronium. Anaesth Analg. 2004;98:193-200
27. Murphy GS et al. Impact of shorter-acting neuromuscular blocking agents on fast-track recovery of the cardiac surgical patient. Anesthesiology 2002;96(3):600-6
28. Norton M et al. Residual neuromuscular block as a risk factor for critical respiratory events in the post anesthesia care unit. Rev Esp Anestesiol Reanim. 2013 Apr;60(4):190-6
29. Murphy GS and Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg. 2010;111(1):120-8
30. Hayes AH et al. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia 2001;56(4):312-8
31. Baillard C et al. Residual curarization in the recovery room after vecuronium. Br J Anaesth. 2000;84(3):394-5
32. Esteves S et al. Incidence of postoperative residual neuromuscular blockade in the postanaesthesia care unit: an observational multicentre study in Portugal.Eur J Anaesthesiol. 2013 May;30(5):243-9
33. Wilson J et al. Residual neuromuscular blockade in critical care. Crit Care Nurse 2012;32(3):e1-9
34. Naguib M et al. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth. 2007;98(3):302-16
35. Yip PC et al. Incidence of residual neuromuscular blockade in a post-anaesthetic care unit. Anaesth Intensive Care 2010;38(1):91-5
36. Phillips S et al. A survey of the management of neuromuscular blockade monitoring in Australia and New Zealand. Anaesth Intensive Care 2013;41(3):374-9
37. Murphy GS et al. Residual paralysis at the time of tracheal extubation. Anesth Analg. 2005;100(6):1840-5
38. Heier T et al. Relationship between normalized adductor pollicis train-of-four ratio and manifestations of residual neuromuscular block: a study using acceleromyography during near steady-state concentrations of mivacurium. Anesthesiology 2010;113(4):825-32
39. Baillard C et al. Postoperative residual neuromuscular block: a survey of management. British J Anaesthesia 2005;95(5):622-6
40. Srivastava A and Hunter JM. Reversal of neuromuscular block. Br J Anaesth. 2009;103(1):115-29
41. Feldman S and Karalliedde L. Drug interactions with neuromuscular blockers. Drug Saf. 1996;15(4):261-73
42. Thilen SR et al. Intraoperative neuromuscular monitoring site and residual paralysis. Anesthesiology. 2012;117:964-972
43. Sterling E et al. Guide to neuromuscular blocking agents. Anesthesiology News Special Edition 2007;25-30
44. Ledowski T et al. Introduction of sugammadex as standard reversal agent: Impact on the incidence of residual neuromuscular blockade and postoperative patient outcome. Indian J Anaesth. 2013;57(1):46-51
45. Karalapillai D et al. Sugammadex. Crit Care Resusc. 2013;15:57-62
46. Abrishami A et al. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Cochrane Database Syst Rev. 2009;4:CD007362
47. Woo T et al. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. Korean J Anesthesiol. 2013;65(6):501-7
48. Ledowski T et al. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: Sugammadex, neostigmine or no reversal. Eur J Anaesthesiol. 2013; Nov 20 [Epub ahead of print]
49. Della Rocca G et al. Reversal of rocuronium induced neuromuscular block with sugammadex or neostigmine: a large observational study. Acta Anaesthesiol Scand. 2013;57(9):1138-45
50. Fuchs-Buder T et al. Is sugammadex economically viable for routine use. Curr Opin Anaesthesiol. 2012;25(2):217-20
51. Butterly A et al. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anaesth. 2010;105(3):304-9
52. Grosse-Sundrup M 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
53. Fuchs-Buder T. Residual neuromuscular blockade and postoperative pulmonary outcome: The missing piece of the puzzle. Eur J Anaesthesiol. 2014;31(8):401-3
54. Saricicek V et al. Does rocuronium-sugammadex reduce myalgia and headache after electroconvulsive therapy in patients with major depression? J ECT. 2014;30(1):30-4

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