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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Neuromuscular Blocking Drugs and Postoperative Pulmonary Complications

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Abstract

Purpose of Review The purpose of this chapter is to provide a brief review of the literature around the relationship between the use of neuromuscular blocking drugs and subsequent postoperative pulmonary complications.

Recent Findings A recent series of retrospective studies evaluating the use of neuromuscular blocking agents and postoperative complications have demonstrated growing evidence for a clear relationship between the use of the agents and downstream complications. The frequency of postoperative respiratory problems seems to be mitigated to some degree through the appropriate use of reversal agents.

Summary Care should be exercised when administering neuromuscular blocking agents during surgical procedures. Appropriate monitoring of neuromuscular transmission should be used along with a strategy to provide adequate reversal at the end of the surgical procedure.

Keywords Neuromuscular blocker · Postoperative complications · Pulmonary · Anesthesiology · Anesthesia reversal · Postoperative pneumonia

Introduction

According to the latest data from the Centers for Disease Control and Prevention, around 51 million inpatient surgical procedures were performed in the USA in 2010, and globally over 187 million surgeries are performed under general anesthesia each year according to the World Health Organization [1]. Non depolarizing neuromuscular blockers are commonly used to facilitate endotracheal intubation as well as to maintain skeletal muscle relaxation during the surgical procedure.

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

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History of Neuromuscular Blockers

The introduction of neuromuscular blocking agents has revolutionized the practice of anesthesia and surgery. D-tubocurarine, derived from curare was the first neuromuscular blocking agent used in clinical practice [2]. Although curare had been in use by the Indians in the Amazon region for centuries as a poison on the tip of their arrows for hunting, its mechanism of action and clinical use was not discovered until the eighteenth century. Sir Henry Dale and his colleagues determined that acetylcholine (Ach) was the transmitter at the neuromuscular junction. One of the first reported uses of D-tubocurarine was by Harold Randall Griffiths from Montreal Canada in 1942 [3]. Later, John Halton and Cecil Gray from Liverpool used curare on a large series of patients during surgery and reported their experience in 1946 [4]. In 1947, Daniel Bovet developed the first synthetic neuromuscular blocker, gallamine, a trisquarternary compound which was followed by the introduction of suxamethonium [5]. Suxamethonium or succinylcholine, is a quaternary ammonium compound which is a short acting depolarizing neuromuscular blocking agent (NMBA). The long-acting non depolarizing NMBA, pancuronium, was introduced shortly afterwards, followed

by the intermediate-acting agents vecuronium, atracurium, cis- atracurium, and rocuronium. Non- depolarizing NMBAs competitively block the acetylcholine at the postsynaptic receptors on the motor end plate. At the present time, vecuronium and rocuronium are the most commonly used NMBA to facilitate tracheal intubation and maintain optimal surgical conditions.

Monitoring Neuromuscular Blockade

The depth of neuromuscular blockade can be monitored using subjective or objective monitoring (i.e., acceleromyography). Train-of-four (TOF) stimulation is the most common mode of monitoring in clinical practice [6]. Train-of-four stimulation is a way of measuring the depth blockade when four successive stimuli are delivered at 2 Hz and muscle contractions in response to a peripheral nerve stimulation such as ulnar nerve at the wrist are observed or measured [7].

The ratio of the height of the fourth response to the first has been defined as the train-of-four ratio. In the absence of non-depolarizing block, the T4/T1 ratio is approximately one. There are a variety of commercially available devices routinely used in practice to assess blockade adequacy and reversal [6].

Neuromuscular Blockade and Postoperative Complications

The expected course of neuromuscular blockade is reversal at the end of the case as a part of the standard anesthetic plan. However, most clinicians do not routinely antagonize NMBAs. Not surprisingly, residual neuromuscular blockade is a common complication in the postoperative phase of care following the use of a non-depolarizing neuromuscular blocking agent (NMBA) with a reported incidence ranging 26–88% [8]. A more recent meta-analysis examining the effect of intraoperative monitoring of neuromuscular blockade on postoperative residual blockade reported residual block in approximately 41% of patients [9]. Residual NMB is defined as TOF < 0.9 which is associated with increased risk of postoperative respiratory complications resulting from impaired pharyngeal function, increasing the risk of aspiration, and pneumonia [10]. Additional complications are listed in Table 1.

Table 1 Complications associated with neuromuscular blockade

Pulmonary	Hypoxemia Airway obstruction Pneumonia Aspiration
Neurologic	Muscle weakness Awareness during extubation
Other	Delayed discharge Prolonged length of stay

Reversal of Neuromuscular Blockade and Postoperative Complications

Three recent large retrospective studies and one prospective study have all explored the relationship between reversal of neuromuscular blockade and postoperative complications.

The first study estimated the incidence of post-operative complications associated with use of neuromuscular blockade through an evaluation of adult non-cardiac surgical patients [11•]. In this retrospective evaluation, the authors evaluated a cohort of 128,886 patients who had received a neuromuscular blocking agent between April 2005 and December 2013. The study measured the incidence of major and minor post-operative complications in the post anesthesia care unit comparing patients who received reversal of neuromuscular blockade to those who did not. The authors reported that the incidence of any major complications was 2.1%. Additionally, the ICU admission rate was 1.3% in patients without any complications, versus 5.2% in patients with any minor complications. Patients who received reversal of the neuromuscular blocking agent with neostigmine had a lower incidence of any major complication (1.7 vs. 6.05%), rate of re-intubation (0.8 vs. 4.6%), and unplanned ICU admission (0.8 vs. 3.2%) compared to patients who did not receive reversal. The authors concluded that patients receiving reversal were at a lower risk of re-intubation and unplanned ICU admission, suggesting a justification for routine use of reversal agents.

The second study evaluated 11,355 adult patients undergoing general anesthesia for noncardiac surgery at five Veterans Health Administration hospitals [12•]. The primary outcome in this evaluation was a composite of respiratory complications (failure to wean from the ventilator, reintubation, or pneumonia).

The authors found that administration of neuromuscular blockade without neostigmine reversal was associated with increased odds of respiratory complications (PM odds ratio [OR], 1.75 [95% confidence interval [CI], 1.23–2.50]; MLR OR, 1.71 [CI, 1.24–2.37]) and a marginal increase in 30-day mortality (PM OR, 1.83 [CI, 0.99–3.37]; MLR OR, 1.78 [CI, 1.02–3.13]). Interestingly, in this study, there was no statistically significant association with nonrespiratory complications or long-term mortality. The authors of this study concluded that the use of neuromuscular blockade without neostigmine reversal was associated with increased odds of poor respiratory outcomes.

A third study evaluated if intermediate-acting neuromuscular blockade use was associated with postoperative pneumonia and if that association was mediated by the use of a reversal agent [13••]. In this study, 13,100 adult surgical cases from the

Vanderbilt University Medical Center were evaluated. The authors used a propensity score-matched model to compare surgical patients who received reversal with neostigmine to patients who did not. Those authors found that patients receiving neuromuscular blockade had a higher absolute incidence rate of postoperative pneumonia (9.00 vs. 5.22 per 10,000 person-days at risk), and the IRR was statistically significant (1.79; 95% bootstrapped CI, 1.08 to 3.07). Among surgical patients who received neuromuscular blockade, patients who were not reversed were 2.26 times as likely to develop pneumonia after surgery compared to cases who received reversal with neostigmine (IRR, 2.26; 95% bootstrapped CI, 1.65 to 3.03). The authors of this study concluded that intraoperative use of intermediate-acting nondepolarizing neuromuscular blocking agents was associated with development of pneumonia after surgery and among patients who received those agents; nonreversal was further associated with an increased risk of postoperative pneumonia.

A four trial, which was prospective, examined the incidence of postoperative residual blockade and the development of respiratory complications [14•]. In this study, the authors examined an observational cohort of 558 patients that underwent general anesthesia with neuromuscular blockade. The authors divided the patients into groups that had received cisatracurium, cisatracurium-neostigmine, rocuronium, and rocuronium-sugammadex. In their results, the authors report that 27.9% had residual blockade in the post anesthesia care unit (cisatracurium 34%, cisatracurium-neostigmine 28.6%, rocuronium 34%, and rocuronium-sugammadex 1.15%). The incidence of major adverse respiratory events was 7.5%. These events were more common in patients with postoperative residual blockade.

Reversal with Sugammadex

The recent availability of sugammadex has significantly modified practice around the use and reversal of neuromuscular blockade. This new selective relaxant-binding agent, sugammadex, is able to reverse any depth of block from aminosteroid (but not benzylisoquinolinium) relaxants [15]. One study has evaluated the impact of sugammadex on postoperative neuromuscular blockade and respiratory outcomes [16]. In this retrospective analysis, the authors evaluated 1444 patients from a teaching hospital in Western Australia who received at least one dose of a non-depolarizing muscle relaxant intraoperatively. In this analysis, 722 patients received reversal with sugammadex, 212 with neostigmine, and 510 received no-reversal. The authors found that the incidence of postoperative nausea and vomiting was higher in neostigmine-reversed than sugammadex-reversed patients (21.5 vs. 13.6%; $P < 0.05$). There was no difference found regarding other variables such as PACU length of stay or hospital stay. The study was not conclusive regarding the relationship between pulmonary outcomes and reversal agent, but the authors suggested that sugammadex may reduce the risk of pulmonary complications in elderly patients with comorbid disease.

Strategies to Avoid Postoperative Complications

A variety of strategies to avoid postoperative complications associated with use of neuromuscular blocking agents have been suggested. First, the use of long-acting agents should be avoided whenever possible. For example, after an intubating dose, the duration of action for pancuronium is 60–120 min compared to 35–50 min for cisatracurium. Second, avoid the use of deep blockade where the train of four count is zero, unless absolutely indicated for the surgical procedure. Third, use neuromuscular blockade monitoring to guide dosing and reversal of neuromuscular blocking drugs is mandatory. One recent study found that almost 25% of patients receiving neuromuscular blocking drugs had no documentation of any neuromuscular monitoring [17]. Ideally, quantitative monitoring should be applied whenever a NMBA is administered. Fourth, ensure that adequate reversal of neuromuscular blockade has been achieved prior to tracheal extubation. This can be accomplished either through spontaneous recovery without the use of a reversal agent, or through the use of neostigmine or sugammadex. However, clinicians should be aware that spontaneous recovery can be quite prolonged and variable.

One center recently described a study to assess the effect of a neuromuscular monitoring e-learning module on anesthesia staff's use of objective neuromuscular monitoring and the incidence of residual neuromuscular blockade in surgical patients at six Danish teaching hospitals [18]. The authors have published their e-learning module, but not the results of the intervention.

Summary and Conclusions

There is growing evidence that use of neuromuscular blockade can lead to postoperative complications. Given the large practice shift occurring with the adoption of sugammadex, it is unclear how the incidence or severity of these complications may shift. Nonetheless, appropriate use of neuromuscular blockade monitoring and strategies to avoid postoperative complications are both warranted.

Compliance with Ethical Standards

Conflict of Interest Letha Mathews and Jesse M. Ehrenfeld declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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