



Investigation of intraoperative dosing patterns of neuromuscular blocking agents

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Abstract

There is a growing body of literature documenting the use of deep neuromuscular block (NMB) during surgery. Traditional definitions of depth of NMB rely on train-of-four assessment, which can be less reliable in retrospective studies. The goal of our study was to investigate the real-world practice pattern of dosing of neuromuscular blocking agents (NMBA), utilizing the amount of NMBA used during the course of a case, adjusted for patient weight and case duration, as a surrogate measure of depth of NMB. We also aimed to identify case factors associated with larger NMBA doses. In this retrospective observational analysis of our anesthesia information management system, we analyzed all general endotracheal anesthesia cases from 2012 to 2015 in which an intermediate-acting NMBA was used. Cases using a long-acting NMBA or only succinylcholine were excluded. The expected duration of the case was calculated based on the cumulative dose of NMB used, normalized to the patient's ideal body weight and the ED95 of the drug. If the expected duration of the case was greater than the actual case duration documented in the case record, it was classified as higher dosing (HD). If the expected duration was equal to or less than the actual duration, it was considered predicted dosing (PD). Categorical comparisons between HD and PD groups were made for various patient, procedural, and provider factors. 72,684 cases were included in the final analysis, of which 46,358, or 64% of cases, used HD. Cases with patients who were morbidly obese, younger than 65 years, and who were lower ASA Physical Status classification (I or II) used more HD as opposed to PD. Cases that were non-open, used total intravenous anesthesia, emergent cases, or used non-rapid sequence anesthesia induction had higher rates of HD than their matched counterparts. All results were statistically significant. HD was more common in cases that documented train-of-four and used the reversal agent neostigmine. Approximately two-thirds of general endotracheal anesthesia cases using an intermediate-acting NMBA used HD. Cases with higher rates of HD may be those that are traditionally technically complex or emergent, would benefit from greater paralysis, or do not use adjunctive medications for muscle relaxation. Age greater than 65 years was shown to have lower rates of HD, likely due to provider awareness of age-related changes in pharmacokinetics and pharmacodynamics. Intraoperative monitoring and NMB antagonism with neostigmine were used more frequently with HD.

Keywords Neuromuscular blockade · Paralysis · Surgery · Reversal · Depth · Anesthesia · Monitoring

1 Introduction

Neuromuscular blocking agents (NMBAs) are ubiquitous in operating rooms around the world, providing significant clinical benefits including paralyzing all voluntary and reflex muscle movements, improving surgical conditions, reducing the amount of anesthetic needed, decreasing post-operative pain scores, and allowing full control of a patient's respiratory efforts [1–4]. Recent studies have shown, though, that nearly 1% of all general anesthetic procedures have inadequate neuromuscular block (NMB) resulting in procedural interruption [5].

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Recently there has been increased interest in deep [commonly defined as a posttetanic count of 1 or 2, but a train-of-four (TOF) count of zero] versus moderate NMB (TOF counts of 1–2). Several studies have been published stating deep blockade has advantages, including improved respiratory dynamics during assisted ventilation and improved surgical conditions [3, 4, 6–9]. Yet, it is known that larger doses and repeated administration of NMBA takes longer to reverse given a prolonged duration of action [10–13]. Traditionally, a non-depolarizing NMB could only be antagonized with acetylcholinesterase inhibitors, such as neostigmine, which could safely reverse only moderate block. This could lead to delays if an anesthesia provider needed to wait for a patient to recover from deep to moderate block before reversal. With the clinical availability of the direct reversal agent sugammadex since 2016, first in Europe and now in the United States, even deep NMB can now be reversed. Evidence has shown its use can provide a more predictable recovery and eliminate residual neuromuscular blockade, lead to shorter recovery times, decreased incidence of prolonged intubation, and may even help increase patient throughput, although the impact on cost is based on individual organizational factors [14–18]. The availability of sugammadex will likely lead to further changes in clinical practice, and its impact on patient outcomes and costs is still being studied.

Despite the known benefits deep NMB can provide and the advent of novel agents that can make it cost and time effective, little research has been done to assess the real world use of a deep NMB. While clinical practice suggests deep NMB occurs frequently, based on the existing literature there has not yet been a quantitative assessment for the exact intraoperative prevalence of deep NMB. Also, while a definition of deep block based on TOF as defined above or qualitative assessment methods is useful for prospective trials, in clinical practice and observational studies it is less practical. While more providers are using a TOF to assess the depth of anesthesia, this is not always documented clearly in the record and may not be universal practice, with other providers only assessing TOF to determine when to redose NMBA or reverse the NMB. Thus, if a deep level of NMB is being used but TOF is monitored or at least recorded too late when multiple twitches have already returned, in retrospective studies this would be classified incorrectly as moderate NMB, providing a falsely low prevalence of deep NMB in clinical practice. A surrogate definition that can be obtained retrospectively from medical records based on the amount of NMBA administered is needed.

The goal of our study is to investigate the real world practice pattern of dosing of NMB, utilizing the amount of NMBA used during the course of a case, adjusted for patient weight and case duration, as a surrogate for depth of NMB. Using this definition that can be more accurately applied to

a retrospective study, we aimed to determine the prevalence rate of cases that used a larger adjusted dose of NMB and the associated patient and procedure factors that could help identify cases that may use a deeper block. In addition to increasing provider awareness, these data would also be used to inform pharmacoeconomic models, including those for newer direct reversal agents.

2 Materials and methods

2.1 Data source

We retrospectively collected intraoperative data on surgical cases from 2012 to 2015 at the Brigham and Women's Hospital, a 773-bed, tertiary care academic center. The anesthesia providers documented each case in the intraoperative anesthesia electronic health record (EHR) system, MetaVision® (iMDsoft, Düsseldorf, Germany), and a research assistant transferred the data from MetaVision® to an electronic database. This database meets criteria of the Health Insurance Portability and Accountability Act to protect personal information. All patient data were de-identified and aggregated for analysis. Due to the retrospective and de-identified nature of this study, our institutional review board provided an exemption from the consent requirement.

2.2 Study sample

Database selection included all general endotracheal anesthetic cases from 2012 to 2015 at one institution, which covered 90,479 cases. Of these, cases that used an intermediate-acting NMBA (including vecuronium, cisatracurium, or rocuronium) at least once were selected (88,355 cases). Cases that used only succinylcholine or used a long-acting NMBA (e.g. pancuronium) were excluded. From the cases, the following variables were collected: age group (categorized into age < 18, 18–49, 50–64, 65–79, 80+), gender (categorized into male or female), body mass index (BMI) (categorized into BMI group < 18, 18.0–24.9, 25.0–29.9, 30.0–39.9, and ≥ 40.0), American Society of Anesthesiologists (ASA) Physical Status classification, emergency status of surgery, use of inhalational versus total intravenous anesthesia, rapid sequence induction (true or false), use of reversal agent neostigmine (true or false), train of four (TOF) recordings (range 0–4), case duration, surgical technique (open vs. minimally invasive, including laparoscopic and thoracoscopic), and surgical subspecialty (Tables 1, 2). Any case with missing data for any of the above variables was excluded from the analysis for that variable. Cases with extreme outliers for ideal body weight (IBW), defined as < 27 or > 270 kg, were excluded from analysis due to likely erroneously entered values. In addition, any case with a

Table 1 Demographics of patients included in the final analysis

Patient demographic	Number of patients	Percentage of total (%)
Age group		
< 18	157	< 1
18–49	24,272	33
50–64	23,800	33
65–79	19,523	27
80+	4930	7
Missing	2	< 1
ASA-PS Classification		
I–II	30,178	42
≥ III	34,381	47
E	3201	4
Missing	4924	7
Gender		
Male	30,441	42
Female	42,239	58
Missing	4	< 1
BMI		
< 18.0	1811	2
18.0–24.9	20,975	29
25.0–29.9	23,766	33
30.0–39.9	20,126	28
≥ 40.0	5,944	8
Missing	62	< 1
Total cases	72,684	

ASA-PS American Society of Anesthesiologists-Physical Status Classification, *E* emergent, *BMI* body mass index

description of “procedure cancelled” was excluded. Cases with missing timestamps for “ready to close” or incision time, or those cases with the exact same time stamp, were also excluded from analysis. After exclusion, 72,684 cases remained. Of note, the time period studied was prior to the introduction of sugammadex at our institution, and only neostigmine was available to anesthesia providers for NMB reversal.

2.3 Statistical analysis

The dosing level of neuromuscular blockade (NMB) used was measured by the amount of intermediate-acting non-depolarizing neuromuscular blocking agent used in the actual duration of the case compared to the “expected” duration. To normalize doses of intermediate-acting NMBA used across all patients in the dataset, we employed a methodology that adapted a previously published composite variable that adjusts NMBA doses based on ideal body weight (IBW) [10, 19]. For each patient, IBW was calculated based on the Devine formula, unless the height

Table 2 Case characteristics of those procedures included in the final analysis, including surgical service type, case type, anesthesia type, and induction type

Case characteristic	Number of patients	Percentage of total (%)
Service		
Anesthesiology/pain	453	1
Bone marrow transplant	170	< 1
Burn trauma	4305	6
Cardiology	563	1
Cardiac surgery	5703	8
General and gastrointestinal	9524	13
Gynecology	9892	14
Neurosurgery	5446	7
Orthopedics	10,278	14
Oncologic surgery	4739	7
Otorhinolaryngology	1505	2
Plastics	3734	5
Renal transplant	705	1
Thoracic	9361	13
Urology	3436	5
Vascular	2517	3
Other	353	< 1
Case type		
Open	51,911	71
Non-open*	20,773	29
Anesthesia type		
Volatile	68,201	94
TIVA	4483	6
Induction type		
RSI	5007	7
Standard	67,677	93

*Non-open cases includes laparoscopic and thoracoscopic cases
TIVA total intravenous anesthetic, RSI rapid sequence induction

was less than 152.4 cm, in which case the patient’s actual body weight (ABW) was used. Next, the median dose required per unit of IBW to achieve a 95% decrease in maximal twitch response from baseline in 50% of the population (ED95) was obtained for each NMBA. Then, the cumulative dose for each NMBA per case was calculated and divided by the ED95 for each NMBA and the patient’s IBW. The “expected duration” of the case was calculated by assuming the average duration of neuromuscular blockade that would be expected based on the ED95 dosing (e.g. 25 min for vecuronium, 30 min for rocuronium, and 30 min for cisatracurium) multiplied by the ED95-adjusted amount of blockade used during the case. The actual duration of the case was obtained from the surgical record, defined as the difference between surgical incision time and “ready to close” time. Any case whose expected duration was greater than the actual duration was classified as

using higher dosing (HD). If the expected duration was less than or equal to the actual duration of the case, it was classified as predicted dosing (PD).

The percent of cases per category, stratified by patient and case characteristics, that used HD were calculated. The characteristics analyzed included BMI classification, age focusing on the elderly (defined as age greater than 65 years), surgical specialty, non-open (e.g. laparoscopic) versus open surgery, emergent cases, rapid sequence induction (RSI), total intravenous anesthetic (TIVA) versus use of volatile agent, documentation of TOF at least once, and use of reversal agent neostigmine. Data were imported into JMP® Pro, Version 12 (SAS Institute Inc., Cary, NC) for statistical analysis. Categorical comparisons were made with Pearson’s Chi squared test, and a Bonferroni correction was conservatively applied to reduce the possibility of type I error with increasing number of comparisons. This resulted in an adjusted p value of 0.006 (0.05 divided by the nine comparisons made).

3 Results

A total of 90,479 cases were performed with general endotracheal anesthesia with documented “induction complete” and surgery end times from 2012 to 2015. A total of 88,355 of these cases had documentation of an intermediate-acting NMBA used at least once. After applying exclusion criteria outlined in the Methods section, data from 72,684 cases were included for final analysis. A description of baseline patient characteristics is found in Table 1 and a list of intraoperative characteristics is found in Table 2. The total number of cases in our final analysis that used HD was 46,358, or 64% of all cases.

Patient groups that used a greater proportion of HD compared to PD had a higher BMI, age younger than 65, and lower ASA Physical Status classification score (Fig. 1). HD was used 11% more often with morbidly obese patients versus patients with a normal BMI. The incidence of HD in elderly patients over the age of 65 was slightly lower but

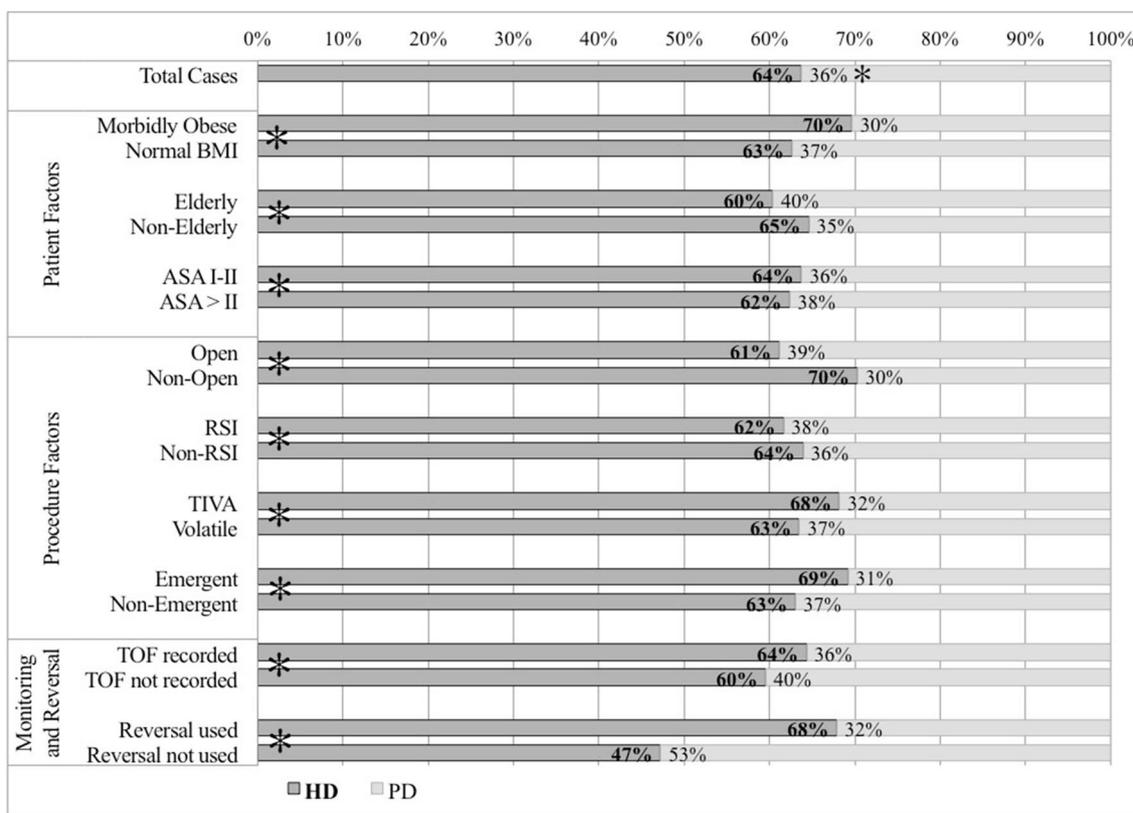


Fig. 1 Use of HD versus PD stratified by patient and procedure factors. HD was used more frequently in morbidly obese patients (BMI > 40) compared to patients with normal BMI (18–24.9), in non-elderly patients (defined as less than 65 years old), and in patients with a lower ASA physical status class (I and II). HD was used more often in non-open (including laparoscopic and thoracoscopic cases) compared to open cases. Anesthetic related factors associated with

HD were non-RSI, TIVA, and emergent cases. HD was used more often in cases where TOF was recorded at least once and where the reversal agent neostigmine was used. All data were statistically significant (*p < 0.001). HD higher dosing, PD predicted dosing, BMI body mass index. Elderly defined as age greater than 65 years old. ASA American Society of Anesthesiologists, RSI rapid sequence induction, TIVA total intravenous anesthetic, TOF train-of-four ratio

similar compared to non-elderly (60% in elderly vs. 65% in non-elderly). Similar results were seen even with higher age cutoffs (70 or 80 years, etc.). HD was used slightly more often in patients with lower ASA Physical Status classification (64% in ASA I–II, 62% in ASA > II). All results were statistically significant with $p < 0.001$.

Procedures shown to have a higher proportion of HD included non-open cases, use of total intravenous anesthetic (TIVA), emergent cases, and non-rapid sequence inductions (Fig. 1). The largest difference was seen related to surgical case type, as would be expected, with non-open cases associated with HD 13% more often than open surgical cases. Assessing the relationship of anesthetic choice with HD, 68% of TIVA cases used HD versus 63% of cases that used a volatile anesthetic. Cases classified as emergent used HD 69% of the time, slightly higher than the 63% in non-emergent cases. HD was seen more in cases that did not use rapid sequence induction (64% with non-RSI vs. 62% with RSI). All results were statistically significant with $p < 0.001$.

With respect to surgical specialty (Fig. 2), HD was used in approximately two-thirds of all surgical cases. Cases booked under the renal transplant service had the highest proportion of HD (81%), with cardiology cases being the next most common at 79%. Otorhinolaryngology, surgical oncology, and cardiac surgery had the lowest incidence of HD use, but still had approximately half of patients receiving HD in each.

Provider trends were also analyzed to determine real-world assessment of depth of neuromuscular blockade and use of the reversal agent neostigmine (Fig. 1). Similar proportions of cases using HD were found in cases that recorded TOF (64%) and did not record TOF (60%). However, HD was more frequent in cases that used the reversal agent neostigmine (68%) than in cases that did not use reversal (47%).

4 Discussion

Our study found certain patient, procedure, and service factors that tended to be associated with higher adjusted dosages of NMB administered by anesthesia providers during surgery. Two major patient-specific factors were found in cases that used HD. One was higher BMI class, which was particularly notable given a known increased incidence of respiratory comorbidities, such as obstructive sleep apnea, and other related complications in patients with higher BMIs [20, 21]. Possible explanations for the larger doses of NMBA used in our study could be due to surgery being more difficult in these individuals or increased patient-ventilator dyssynchrony given the resistance of the diaphragm and abdominal wall muscles to the effects of the NMBA, necessitating larger doses of NMBA being used [10]. Some anesthesia providers may also have incorrectly used actual

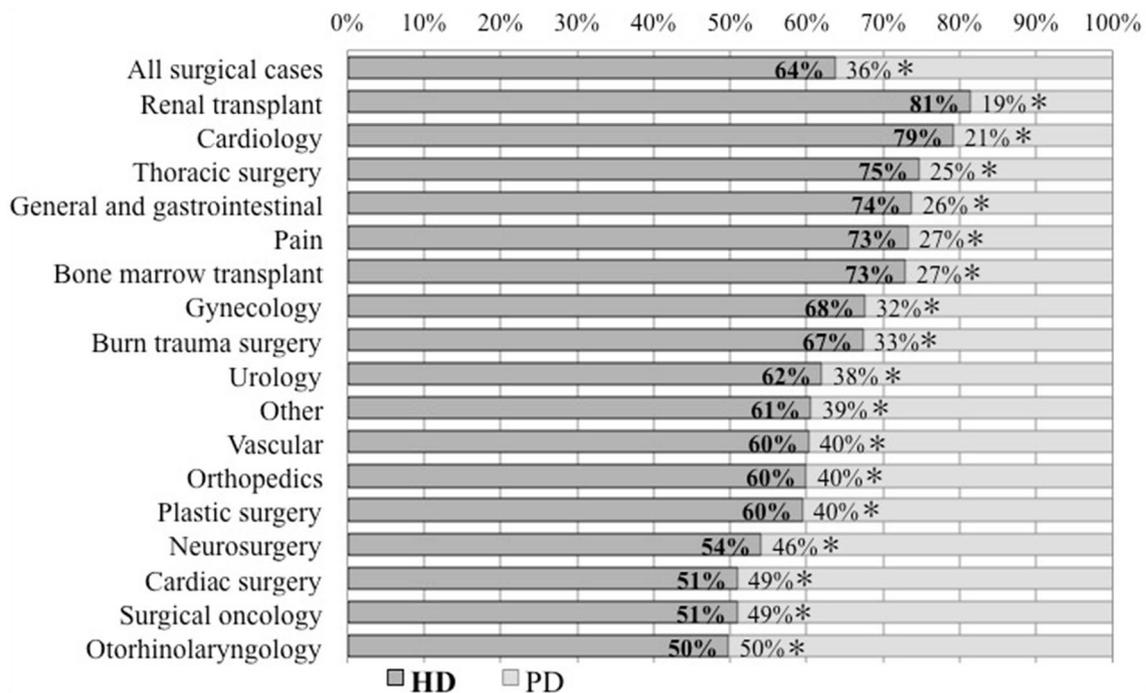


Fig. 2 Surgical service trends of HD versus PD neuromuscular blockade. The services with the greatest percentage of HD were the renal transplant service and cardiology service. The services with

the lowest percentage of HD were otorhinolaryngology, surgical oncology, and cardiac surgery. All data were statistically significant ($*p < 0.001$). HD higher dosing, PD predicted dosing

body weight as opposed to ideal body weight for calculations of NMBA dosage to use, leading to larger dosages used. Another possibility could be patients with higher BMI undergoing types of surgeries that themselves are associated with HD, leading to a potential confounder. The second patient-related factor associated with HD was younger age, perhaps due to provider recognition for the need for less agent in older patients who would be expected to be more sensitive to, or have increased effects with similar doses, as well as decreased clearance rates compared to younger patients due to age-related changes in pharmacodynamics and pharmacokinetics [22, 23]. Cases with higher ASA Physical Status classification were less likely to use HD, possibly due to the desire of the anesthesia provider to minimize use of NMBA as much as possible in patients with more comorbidities.

The procedure-related factors related to HD were cases that were non-open, used TIVA, booked as emergent, or non-RSI. Non-open cases, including laparoscopic or thoracoscopic cases, used HD more often than open cases, possibly due to the desire for more complete paralysis of the wall musculature and diaphragm, which has been shown to improve surgical conditions during insufflation as well as to patient-ventilator synchrony [1, 4, 8]. Cases scheduled as emergent, which would be for more critically ill patients or time-sensitive pathologies, likely had more HD than non-emergent cases to ensure optimal surgical conditions as much as possible, as well as likely less hesitation on the part of the anesthesia provider to use deeper block as patients are more likely to remain intubated after an emergent than non-emergent case. The higher proportion of TIVA cases with HD is an interesting finding, and may be due to the lack of potentiation from volatile anesthetics, thus requiring additional dosing of NMBs [24]. Non-RSI cases used more HD than RSI cases. This could be due to a large intubating dose of non-depolarizing agent used at the beginning of the case for non-RSI anesthetics, as opposed to succinylcholine for intubation followed by the same small doses of NMBA for maintenance of paralysis. In RSI cases where non-depolarizing agents were used, the even larger dose of NMBA at the beginning could have led to less NMBA redosing for maintenance and overall a smaller dose of non-depolarizing agent used compared to non-RSI cases.

It is difficult to surmise why certain surgical services have a greater proportion of HD compared to PD than others, given that the types of cases can be quite variable. Also, additional factors, such as specialty provider practices or surgeon preference, may play a role as well, adding additional complexity. Some generalizations can be made. Cases where patient movement can be more of an issue, such as thoracic surgery or interventional cardiology procedures (including electrophysiology cases), could be the reason for HD. Similarly, in certain cases, a deeper blockade may be

needed to paralyze the more resistant muscles, including the abdominal wall and diaphragm [25]. Otorhinolaryngology and neurosurgery may have lower rates of HD as more cases may require specialized monitoring that precludes HD (or sometimes any neuromuscular blockade) from being used (of note, all cases included had to use an intermediate acting-NMBA at least once, but could have used a small intubating or even defasciculating dose of NMBA). Also, there are likely factors we have addressed above that are more prevalent in some surgical services compared to others, such as surgical oncology and cardiac surgery possibly having more open procedures than gynecology or general surgery, which can introduce additional confounders.

Looking at the use of monitoring of TOF and reversal of blockade, HD was used more often in cases that recorded TOF and that were reversed, suggesting that providers likely have an awareness of when larger dosages of NMBA have been used. A larger proportion of HD in cases using TOF monitoring may be due to providers' increased awareness of the depth of blockade being used perioperatively, as opposed to using other methods for clinical assessment that may underestimate the depth of block [26]. It should be noted, though, that TOF was not documented in the EHR in all cases regardless of the dose of NMBA. This could be from providers forgetting to document in the EHR, or a true lack of monitoring of TOF. This again emphasizes the need as stated above for a surrogate definition that can be applied to retrospective studies such as this one when TOF may not be assessed immediately after NMBA is administered to determine depth of blockade or may not be monitored at all. Neostigmine reversal was also not used in all cases, for either HD or PD cases. It may be that for some of these cases the majority of NMBA had been administered at the beginning of the case and providers felt patients had achieved enough spontaneous recovery of neuromuscular function to not warrant reversal. While administration of neostigmine after spontaneous recovery may adversely affect neuromuscular function and has its own side effects, omitting reversal even after a single dose of NMBA can introduce a significant risk of residual paralysis and is associated with an increased risk of adverse respiratory outcomes [27–29]. Recent studies show the incidence of residual neuromuscular blockade could be up to 63.5%, stressing the importance of close intraoperative monitoring of NMB [30].

This study has several limitations. Given the retrospective nature of the study, it is prone to the traditional disadvantages of such studies. Our metric of measuring the adjusted dose of NMBA given as a surrogate for depth of neuromuscular blockade also has its imperfections. The variability of the rate of metabolism of NMBAs, particularly rocuronium, has been well documented. In the case of rocuronium, recent studies have shown this may be due to differences in biliary excretion as well as genetic polymorphisms leading

to reduced clearance; thus the same dose of NMBA may produce a deep blockade for some patients but only a moderate blockade for others [31, 32]. Despite this, however, the assessment used here has benefits for applicability to retrospective data. Accurate TOF data are not always available to assess depth of blockade, and as seen from our results some cases that used a NMBA did not have even one recording of TOF. This makes it difficult to validate this metric against standard TOF assessment for depth of NMB outside of conducting a formal prospective trial, as TOF monitoring is largely dependent on provider practices. If, for example, providers only assess TOF to check for the need to redose NMBA intraoperatively or to reverse, TOF may not reflect the depth of blockade and could provide a falsely low proportion of cases that use deep NMB. The surrogate measurement illustrated here provides a more feasible metric for reviewing data retrospectively from an electronic database.

Our study also did not assess when doses of NMBA were given, only the total amount of NMBA used over the course of the case. Short cases were more likely to be defined HD, as the intubating dose of NMBA makes up the majority of agent used over the course of the case and does not reflect the level of blockade for the remainder of the case. Studies have shown that shorter case durations were associated with increased risk for residual block [33]. Finally, given open cases have generally been replaced by minimally invasive, non-open approaches, those patients who had open operations may have distinctive characteristics, such as increased comorbidities or be emergent cases, which could be independent contributing factors for the dosage of NMB used.

5 Conclusion

The frequency of HD use in this academic institution was 64%, defined as the expected duration of the case exceeding the actual case duration based on the cumulative doses of NMBA normalized to IBW and ED95 for the drug. Our study demonstrates that HD was used in patients with a higher BMI, ASA physical status I or II, non-open surgery, use of TIVA, emergent, and non-RSI cases. Cases with patients older than 65 years had a lower percentage of HD, although the significance is unclear given the difference in pharmacokinetics in elderly patients. TOF monitoring and neostigmine reversal were seen more often with HD cases, but neither was documented universally in all cases. Awareness of these factors can help providers determine if patients may have received larger dosages of NMBA than would be predicted for a case. This could guide the need for reversal even if clinical signs may suggest spontaneous recovery, the use of direct-acting reversal agents such as sugammadex, or whether additional postoperative monitoring may be required.

Future studies may apply similar guidelines for assessment using data from multiple facilities to better evaluate more general practices, as well as following cases post-operatively to assess for differences in complication rates between HD and PD cases. Further research could also expand to comparing cases before and after sugammadex became clinically available in our hospital. Additionally, validation of this method with the depth of blockade assessed through TOF would be beneficial, particularly given the increased interest in deep versus moderate blockade in the era of direct reversal agents.

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