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Monitoring of Sugammadex Dosing at a Large Tertiary Care Pediatric Hospital

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ABSTRACT

Introduction: Anesthesiologists use sugammadex to reverse neuromuscular blockade (NMB) produced by rocuronium and vecuronium. Its mechanism involves encapsulation of the neuromuscular blocking agent. Sugammadex dosing is based on the depth of NMB, assessed by measuring the train-of-four (TOF). **Methods:** We retrospectively reviewed procedures under general anesthesia in patients older than 1 year of age if they included sugammadex reversal of rocuronium-induced NMB. Documentation of TOF monitoring before and after reversal was noted, along with the dose of sugammadex administered. TOF was considered correctly documented if the anesthesia provider recorded the number of twitches before and after NMB reversal, or if they recorded 4 twitches before NMB reversal. We defined appropriate sugammadex dosing if it was within 10% of the recommended dose for the depth of NMB. We repeated this review after staff education and creating a reminder in the electronic health record system. **Results:** We included 100 patients in the preintervention analysis, of whom 30% had correct TOF documentation. Among patients with TOF assessment before sugammadex administration, the dose was appropriate in 34 of 40 cases. In the postintervention analysis, we reviewed 75 cases and found that correct documentation improved to 45% ($P = 0.024$). Among postintervention cases with TOF documented before sugammadex administration, sugammadex dosing was appropriate in 62 patients. **Conclusion:** Documentation of TOF was low (30%) before intervention and improved to only 45% after the interventions, suggesting that additional interventions are needed. Even before the intervention, with or without TOF documentation, the dose of sugammadex was generally consistent with recommendations. *(Pediatr Qual Saf 2018;3:e113; doi: 10.1097/pq9.0000000000000113; Published online October 9, 2018.)*

INTRODUCTION

Neuromuscular blocking agents (NMBAs) are commonly used during the perioperative period to facilitate endotracheal intubation or provide ongoing skeletal muscle relaxation for surgical procedures. Anesthesiologists often use nondepolarizing NMBAs due to their favorable adverse effect profile and concerns regarding the use of depolarizing agents such as succinylcholine.[1] This preference for nondepolarizing NMBA comes at the cost of a longer duration of action and the potential for residual postoperative effects including skeletal muscle weakness.[1] The prolonged effects of nondepolarizing NMBAs can lead to postoperative complications involving the airway and respiratory function, including hypoxemia, hypoventilation, upper airway obstruction, and postoperative respiratory insufficiency.[2–6] These effects are particularly likely when incomplete reversal of NMB results in residual weakness.[6,7]

Anticholinesterases (neostigmine, edrophonium) are commonly used as reversal agents for NMBAs but are themselves associated with adverse effects, including fasciculation of skeletal muscles, bradycardia, bronchospasm, nausea, and vomiting.[8,9] Furthermore, these agents are only effective when the concentration of the NMBA in the synaptic cleft is relatively low.[8,9] Sugammadex (Bridion, Merck & Co, Whitehouse Station, N.J.) is a novel pharmacologic agent, which was approved for clinical use in December 2015 by the United States Food & Drug Administration. It reverses neuromuscular blockade (NMB) with a novel, noncompetitive mechanism that differs completely from acetylcholinesterase inhibitors, by encapsulating rocuronium or vecuronium. Initial clinical trials have demonstrated several advantages including a

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complete reversal of residual blockade with a limited incidence of residual postoperative weakness.[10–13]

As sugammadex is a novel pharmacological agent, the consistency and appropriateness of its use by anesthesia providers remain unknown. The dosing for reversal of NMB is based on twitch monitoring using the train-of-four (TOF), with recommended dosing of 2, 4, or 16 mg/kg, depending on the degree of NMB.[8,14,15] The maximum dose of 16 mg/kg is recommended in the case of a "cannot intubate – cannot ventilate" scenario immediately following a full dose of rocuronium (1–1.2 mg/kg).

We hypothesized that there was limited adherence to the recommendations for TOF monitoring to guide the dosing of sugammadex. To determine compliance with TOF monitoring and sugammadex dosing recommendations, we conducted a quality improvement project involving a retrospective chart review of sugammadex administration. This baseline review was followed by a second review that occurred 1 year after the first, to determine the efficacy of interventions aimed at improving compliance with monitoring and dosing recommendations.

METHODS

Setting

Data collection and analysis for this study were deemed exempt from review by the Institutional Review Board at Nationwide Children's Hospital as a quality improvement project. Our institution added sugammadex to the formulary for use in the operating room (for reversal of NMB) in April 2016.[16] A grand rounds presentation was held to educate the staff regarding TOF monitoring, dosing regimen, and proper administration. For the preintervention evaluation, all procedures performed under general anesthesia over a 2-week period (November 28 to December 10, 2016) in patients older than 1 year of age were evaluated for inclusion. During this period, departmental staffing for the rooms in question included 4 anesthesiology residents, 12 Student Registered Nurse Anesthesiologists (SRNAs), 7 pediatric anesthesiology fellows, 39 attending pediatric anesthesiologists, and 37 Certified Registered Nurse Anesthesiologists (CRNAs). Cases were selected for analysis if patients received rocuronium followed by sugammadex. Cases involving patients younger than 1 year of age or magnetic resonance imaging studies were excluded as the ability to monitor TOF, or its accuracy is limited in such scenarios. As our institutional practice is generally for the second anesthesiology provider (fellow, resident, CRNA, or SRNA) to provide primary care and administer medications, including sugammadex, cases were excluded if they had been staffed by an attending anesthesiologist alone. Finally, cases were excluded if they had been staffed by study investigators.

Data Collection

Data for included cases were extracted from the electronic medical record, and included patient demographic characteristics (age, sex, and weight), anesthesia provider roles (fellow, resident, CRNA, or SRNA), documentation of depth of NMB (twitch monitoring using TOF) before and after sugammadex administration, and the dose of sugammadex (mg/kg) administered. We defined compliance with TOF documentation as documenting TOF before and after sugammadex administration or documenting 4 responses (twitches) to TOF before NMB reversal. For patients with TOF monitoring documented before sugammadex administration, the secondary outcome was the appropriateness of the sugammadex dose according to the package insert. The recommended dosing is 2 mg/kg for ≥ 2 twitches, 4 mg/kg for 1–2 posttetanic twitches, and the maximum recommended dose, for the immediate reversal of an intubating dose of rocuronium (1.2 mg/kg) in a "cannot intubate-cannot ventilate" scenario, is 16 mg/kg. Based on the above method of calculating the dose, we used a ± 10% margin of error to classify overdosing or under-dosing. We also noted any adverse postoperative respiratory events, including clinical documentation of inadequate reversal of NMB, postoperative reintubation, oxygen desaturation, laryngospasm, bronchospasm, or prolonged need for supplemental oxygen (greater than 1 hour).

Intervention

After obtaining these baseline data on compliance, we shared the overall level of compliance with the faculty and staff, followed by providing departmental-level education that covered monitoring, assessment, and proper dosing regimens. Faculty and staff involved in the project met, and a Key Driver Diagram with the needed intervention was developed (Fig. 1). We ensured the availability of TOF monitors at all anesthetizing locations before proceeding with the intervention. Additionally, to facilitate compliance with documentation and dosing guidelines, a reminder was created in the perioperative electronic health record system to remind the provider to assess twitch monitoring every time they administered an NMBA. Postintervention chart review was undertaken over a 2-week period from October 2, 2017, to October 15, 2017, following the same methodology as above. During this period, the department was staffed by 4 residents, 10 SRNAs, 9 fellows, 41 attending anesthesiologists, and 37 CRNAs. We initiated the second phase of the study (postintervention evaluation) approximately 2 weeks after completing the interventions.

Statistical Analysis

We compared study outcomes across periods (pre- and postintervention) and provider roles using Chi-square or Fisher's exact tests in Stata/IC 14.2 (StataCorp, LP, College Station, Tex.). $P < 0.05$ was considered statistically significant.

RESULTS

During the preintervention review period, 119 patients received sugammadex, of whom we excluded 10 cases

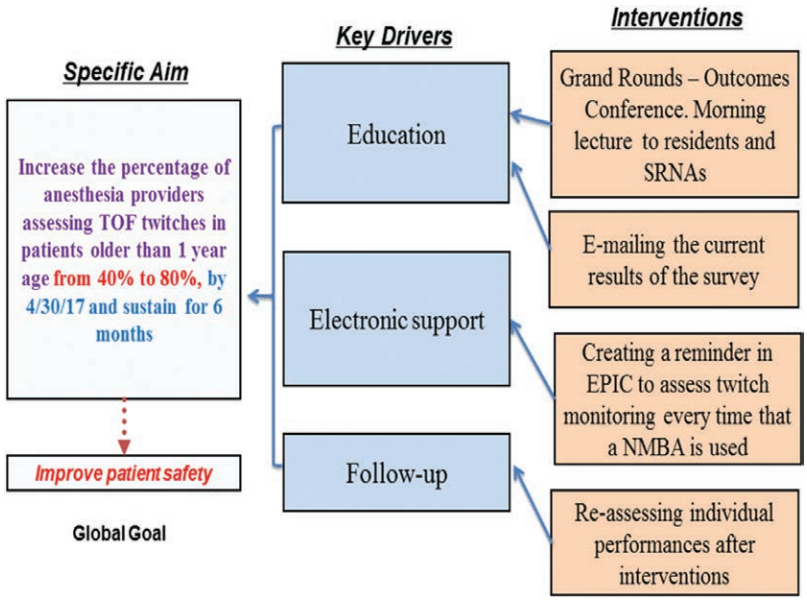

Fig. 1. Key driver diagram showing quality improvement process for the study.

due to age younger than 1 year, 4 cases staffed by a study investigator, 3 cases due to magnetic resonance imaging examination, and 2 cases staffed by an attending anesthesiologist alone. Therefore, we included 100 cases in the preintervention analysis (Table 1). Thirty cases (30%) had appropriate documentation of TOF monitoring and documentation of sugammadex use. This group included 17 patients who had 4 twitches before sugammadex administration and 13 with a documented TOF before and after sugammadex administration. Among 70 cases who did not document TOF appropriately, 10 had a documented TOF with fewer than 4 twitches before sugammadex administration and did not document TOF afterward, 5 had documented TOF only after sugammadex administration, and 55 did not document TOF at all. Among the 40 cases in whom the provider documented presugammadex TOF, sugammadex dosing was appropriate in 34 of 40 cases (85%), was excessive (> 110% of recommended) in 4 cases (10%), and low or under-dosed (< 90% of recommended) in 2 cases (5%). No patient received a second dose of sugammadex, and there were no identified adverse postoperative airway or respiratory events for any of the 100 patients reviewed. There were no differences in the likelihood of documenting TOF or administering the correct dose of sugammadex according to the role of the "hands-on" anesthesia provider (Table 2).

Table 1. Patient Demographics and Dosing of Sugammadex

Categories	Preintervention N = 100	Postintervention N = 75
Age (y)		
0–5	26	16
6–10	20	13
11–15	32	24
16–20	20	15
> 20	2	7
Weight (kg)		
0–20	26	13
21–40	22	22
41–60	26	14
61–80	14	13
> 80	12	13
Sex		
Male	48	48
Females	52	27
Dose of sugammadex administered		
With TOF before (only)	27	45
With TOF after (only)	5	4
With TOF before and after	13	4
Without TOF	55	22

Among 75 postintervention cases in our review, there was a modest improvement in correct TOF documentation to 34 of 75 (45%; $P = 0.024$). Reasons for incorrect TOF documentation included missing TOF before sugammadex administration (26 patients) and < 4 twitches documented before sugammadex administration with no subsequent TOF documentation (15 patients). There was generally no difference in appropriateness of TOF documentation by provider role, except for a higher rate of missing TOF documentation both before and after sugammadex administration among pediatric anesthesiology fellows (Table 3). Among 49 cases where the provider documented TOF before administering sugammadex, the dosing was within suggested guidelines in only 25 cases (51%), compared with 34 of 40 (85%) cases reviewed before the intervention ($P = 0.001$). Among postintervention cases with TOF documented before sugammadex administration, sugammadex dosing was high in 11 cases and low in 2 cases.

DISCUSSION

In this project, we aimed to increase awareness regarding TOF monitoring before sugammadex administration.

Table 2. Preintervention Comparison of Twitch Monitoring by Provider Role

"Hands on" anesthesia Provider*	CRNA (N = 53)	SRNA (N = 29)	Fellow (N = 9)	Resident (N = 9)	*P*
Twitch monitoring before (only) sugammadex administration, n (%)	17 (32)	4 (14)	4 (44)	2 (22)	0.180
Twitch monitoring before sugammadex administration with 4 responses on the TOF, n (%)	12 (23)	4 (14)	2 (22)	1 (11)	0.755
Twitch monitoring after (only) sugammadex administration, n (%)	1 (2)	4 (14)	0	0	0.114
Twitch monitoring before and after sugammadex administration, n (%)	6 (11)	4 (14)	2 (22)	1 (11)	0.786

*Categories are not mutually exclusive.

Table 3. Postintervention Comparison of Twitch Monitoring Documentation by Provider Role

		Hands-on Anesthesia Provider Role				
Documentation		**CRNA (N = 24)**	**SRNA (N = 24)**	**Fellow (N = 14)**	**Resident (N = 13)**	***P***
Appropriate, n (%)	Twitch monitoring before and after sugammadex administration	2 (8)	1 (4)	0 (0)	1 (8)	0.761
	Twitch monitoring only before sugammadex administration with 4 responses on the TOF	10 (42)	11 (46)	2 (14)	7 (54)	0.144
Not Appropriate, n (%)	Twitch monitoring only before sugammadex administration	4 (17)	4 (17)	4 (29)	3 (23)	0.781
	Twitch monitoring only after sugammadex administration	2 (8)	1 (4)	0 (0)	1 (8)	0.761
	No twitch monitoring	6 (25)	7 (29)	8 (57)	1 (8)	0.046

We evaluated provider compliance before and after educational interventions and modification of the electronic medical record. Due to the common use of NMBAs in anesthesia practice, and the potential for multiple adverse effects, reversal agents are required to mitigate these effects. In contrast to acetylcholinesterase inhibitors, sugammadex has demonstrated a decreased incidence of residual NMB, thereby limiting the potential impact on postoperative respiratory function.[10–13] Although the recommended dosing of sugammadex depends on TOF monitoring, our retrospective review found that this was often not documented by anesthesia providers, even after interventions to alert staff to the low compliance with such monitoring, and education regarding the importance of TOF monitoring for determining sugammadex dosing.

TOF monitoring is recommended to guide sugammadex dosing. Higher than recommended doses are generally well tolerated with a limited adverse effect profile.[17–19] In fact, higher doses (≥ 4 mg/kg) may result in more rapid reversal of NMB, and the absence of TOF monitoring may provide a margin of safety to ensure complete reversal of NMB.[13,20] Clinically, sugammadex is accepted as a safe and well-tolerated pharmacological agent even in high doses, although it may be accompanied by minor and nonspecific effects.[2] Significant yet rare adverse effects, including bradycardia and anaphylactoid reactions, are not associated with a higher dosing regimen.[2,21]

In our institution, the providers typically responsible for administering sugammadex are the "hands-on" anesthesia providers (CRNAs, SRNAs, anesthesiology residents, and pediatric anesthesiology fellows), under the supervision of attending anesthesiologists. Our institution added sugammadex to the formulary in April 2016.[16] Before the introduction of sugammadex, an educational program was held to inform anesthesia providers regarding the proper dosing of sugammadex. In conducting the present study approximately 6 months after the introduction of sugammadex to our practice, we found a lack of TOF monitoring and documentation before and after sugammadex administration. In response, the project described here was initiated, and the study investigators informed members of the department regarding the study results and reminded them to record TOF documentation and to dose sugammadex based on the TOF findings. Although compliance increased, it was still only 45%, which we did not consider a clinically significant improvement because most cases still lacked correct TOF documentation.

The limited improvement following our intervention may suggest that ongoing education or additional initiatives may be needed to improve TOF documentation. According to a recent review of quality improvement projects in the perioperative environment, provider education is the most common intervention type, mentioned in 59% of the projects reviewed.[22] Although some projects report improvement in the quality of perioperative care with interventions that include provider education,[23,24] this was not the case in our project. This finding was all the more striking because our project targeted a process (documenting TOF monitoring) entirely within providers' control, rather than a patient safety measure that could have been subject to external factors. One of the potential explanations and a challenge of educating anesthesia providers is that the majority of the "hands-on" providers (who would have been tasked with documenting TOF

monitoring before sugammadex administration) rotate through our institution for limited periods of time (4–8 weeks), thereby necessitating ongoing and repeated educational initiatives. However, the limitations of provider education do not entirely explain our findings, since we had also implemented a clinical decision support tool that did not achieve the desired improvement in documentation compliance. Notwithstanding the lack of substantive improvement in TOF monitoring, we found that errors in sugammadex dosing were uncommon. High dosing was the most common error, whereas only 2 patients in each evaluation period received a dose < 90% of the manufacturer's recommendation based on the degree of NMB.

Some aspects of the intervention and analysis may limit our conclusions, including the short duration of the study periods (2 weeks in each period) and the relatively small cohort size. More time may have provided a more precise estimate of missing documentation for TOF monitoring. A longitudinal design with more than 2 observation periods may have also shown that the postintervention improvement was no greater than typical month-to-month variation in compliance with TOF documentation, potentially strengthening our conclusion that the improvement in the postintervention period was not clinically significant. As this was a retrospective study, we did not directly observe TOF monitoring, and hence it is plausible that the TOF was monitored and yet not documented. Anesthesia providers might not have monitored TOF if they administered the sugammadex dose based on the duration from rocuronium administration until sugammadex administration (lowering the sugammadex dose as this duration increased).

In many cases, the anesthesia provider administers a single dose of the NMBA for endotracheal intubation for a surgical procedure of ≥ 1 hour duration where the risk of the ongoing NMB is limited, thereby resulting in limited risk of adverse effects if they do not monitor the NMB. Furthermore, given the efficacy of sugammadex, the risk of residual paralysis appears to be limited even when TOF is not monitored. During longer cases, dissipation of NMB may have been assumed by some anesthesia providers when spontaneous ventilation returned after rocuronium administration. Our review did not differentiate among cases with a short or long duration between NMBA administration or reversal and did not differentiate among cases using single as opposed to multiple NMBA doses.

Our project was meant only to evaluate compliance for TOF monitoring during sugammadex administration, and we did not collect data to demonstrate whether TOF monitoring is different with the use of conventional agents for reversal of NMB, acetylcholinesterase inhibitors (neostigmine). In the future, it will be helpful to determine if there were obstacles to TOF monitoring. We intentionally excluded patients less than 1 year of age, given the inherent issues related to TOF monitoring in this group. Although we have ensured that TOF monitors are present in all anesthetizing locations, it may be that in some patients, TOF was not monitored due to lack of access to an extremity, related to surgical positioning. Most importantly, there are no data to demonstrate that lack of monitoring increases the risk of adverse respiratory events. This is potentially related to an overall lack of prospective data on complications after sugammadex administration in children. A recent review and meta-analysis of pediatric trials of sugammadex included only 253 patients,[25] so additional prospective studies may provide more robust information about the likelihood of adverse events with sugammadex use. Perhaps the most important question from the perspective of patient safety is whether the lack of TOF monitoring leads to adverse events. Our preliminary data demonstrate that this is unlikely, as we noted no such events in our study cohort. Therefore, it may be appropriate to develop evidence-based medicine to determine the necessity of TOF monitoring for this novel medication. The most likely benefit may be limiting the dose required. As we noted that high dosing was more common than low dosing in our analysis, it may be that limiting the dose using TOF monitoring would primarily affect cost savings. For many patients, however, cost savings may not be realized if only a single vial were needed regardless of whether the provider calculated the dose as 2 rather than 4 mg/kg.

In summary, despite the recommendation for TOF monitoring for appropriate dosing of sugammadex in the reversal of NMB, anesthesia providers often did not record TOF monitoring after the introduction of sugammadex at our institution. The unsatisfactory improvement after our intervention suggests the need for other forms of interventions, such as decision support for the electronic health record, where a reminder will seem on the screen each time sugammadex is selected on "medications," before charting the dose or when removing it from the Pyxis Anesthesia Machine. Furthermore, it may be practical to mandate documentation of TOF monitoring before closing the anesthesia record at the completion of care. Despite such failures, dosing was generally appropriate or high, and no adverse effects related to residual NMB were noted.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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