

Quantitative Train-of-Four Monitoring Using the TetraGraph™ to Evaluate Rocuronium Requirements During Renal Transplantation in a Pediatric Patient

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Abstract

The pharmacokinetics of neuromuscular blocking agents (NMBAs) may be altered in patients with renal insufficiency or failure, including alterations in the volume of distribution or elimination of the primary drug and its metabolites. In this patient population, monitoring of the end-organ effects of NMBAs may be useful to guide initial and subsequent dosing, as well as reversal of neuromuscular blockade. Train-of-four (TOF) monitoring remains the most commonly used technique to monitor the end-organ effect of NMBAs and the neuromuscular junction. Here we present the use of an electromyography (EMG)-based TOF monitor in a 9-year-old boy with end-stage renal disease during intraoperative anesthetic care for renal transplantation. The perioperative management of such patients, including dosing of NMBAs and use of neuromuscular blockade monitoring, is discussed.

Keywords: Neuromuscular blockade; Neuromuscular blocking agents; Rocuronium; Train-of-four monitor; Renal failure; Renal transplantation

Introduction

The use of neuromuscular blocking agents (NMBAs) in patients with renal insufficiency requires careful monitoring of their end-organ effects and attention to dosing due to the al-

tered pharmacokinetics and pharmacodynamics. Agents such as atracurium and cis-atracurium are considered acceptable alternatives in this setting because they undergo non-organ dependent elimination via Hofmann degradation and ester hydrolysis, whereas other agents that are dependent on renal elimination such as rocuronium, may have altered clearance requiring dose adjustments [1, 2].

Rocuronium, a non-depolarizing NMBA, is primarily metabolized and excreted via the liver and bile (75-90%). However, Robertson et al reported that up to 33% of a dose of rocuronium as well as its primary metabolite are eliminated in the urine [3]. Patients with acute kidney injury (AKI) or chronic kidney disease (CKD) can experience prolonged duration of action due to impaired renal clearance, especially during continuous infusions, thereby increasing the risk of postoperative residual neuromuscular blockade (NMB). Given these concerns, patients with CKD or end-stage renal disease (ESRD) may require intraoperative monitoring of NMB to optimize drug administration and prevent residual postoperative NMB [3, 4].

During the intraoperative administration of NMBAs, train-of-four (TOF) monitoring of the neuromuscular junction may be used to judge the efficacy of the initial dose, evaluate the readiness for endotracheal intubation, guide the timing of redosing, and document reversal of NMB prior to tracheal extubation [5-7]. TOF responses following neurostimulation may be evaluated subjectively (qualitatively) with visual observation of the response or objectively (quantitatively) by measuring the number and strength of the twitches in the TOF sequence. Quantitative technology for TOF monitoring includes mechanomyography, acceleromyography, and electromyography (EMG)-based devices. Calibrated, quantitative TOF NMB monitoring has become the new gold standard for assessing neuromuscular function and recovery during anesthesia [8, 9]. However, there is limited experience with the use of these devices in pediatric-aged patients, especially in the setting of renal transplantation in patients with ESRD. We present the use of an EMG-based TOF monitor in a 9-year-old male with ESRD undergoing renal transplantation. The perioperative management of such patients including NMB monitoring and administration of NMBAs is discussed.

Manuscript submitted June 9, 2025, accepted August 19, 2025
Published online September 17, 2025

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doi: <https://doi.org/10.14740/jmc5151>

Table 1. Timeline of Rocuronium Administration and Neuromuscular Monitoring Using EMG and PNS

Time of day	Rocuronium bolus (mg/kg)	Rocuronium infusion rate (mg/kg/h)	EMG TOFC (twitches)	EMG PTC (twitches)	PNS assessment
7:50 am	1.2	0	Not assessed	Not assessed	Not assessed
8:30 am	-	0	0/4	0/20	0/4
8:35 am	0.6	0	0/4	1/20	Not assessed
9:08 am	-	0	0/4	0/20	0/4
9:44 am	-	0	2/4	-	0/4
10:12 am	-	0	4/4	-	0/4
10:18 am	0.6	0	Not assessed	Not assessed	Not assessed
10:21 am	-	0.2	0/4	Not assessed	Not assessed
10:32 am	-	0.2	0/4	Not assessed	0/4
11:10 am	-	0.2	0/4	Not assessed	0/4
11:27 am	-	0.15	0/4	Not assessed	Not assessed
12:01 pm	-	Discontinued	1/4	-	Not assessed

EMG: electromyography; PNS: peripheral nerve stimulator; PTC: post-tetanic count; TOFC: train-of-four count.

Case Report

The patient was a 9-year-old, 29.3 kg boy with ESRD secondary to renal dysplasia, chronic hypertension secondary to renal disease, seizure disorder, and attention deficit hyperactivity disorder. Family history was relevant for dialysis-dependent ESRD in his grandmother due to diabetes mellitus. Past medical history was notable for asthma and environmental allergies. Past surgical history was relevant for bilateral tympanostomy tube insertions and adenoidectomy at 2 years of age, and orchiopexy at 3 years of age. At the age of 7 years, he was diagnosed with impetigo, tinea cruris, and recurrent oral thrush, treated with mupirocin, ketoconazole, and nystatin, respectively. Three months later, he was taken to urgent care for complaints of fatigue, anorexia, and pallor. At that time, a complete blood count revealed anemia with a hemoglobin of 4.3 g/dL and urinalysis that was positive for protein and blood. He was referred to our institution for further evaluation. Laboratory findings indicative of AKI, including elevated blood urea nitrogen and creatinine, hyperkalemia, hypocalcemia, hyperphosphatemia, hematuria, and massive proteinuria, prompted admission to the pediatric intensive care unit (PICU) for continuous renal replacement therapy (CRRT) initiation, later transitioned to hemodialysis (HD). His clinical course was remarkable for seizures in the setting of electrolyte abnormalities, managed with levetiracetam, and an abdominal ultrasound revealing small kidneys bilaterally, suggesting CKD secondary to dysplastic kidneys. Following hospital discharge, he underwent HD for 3 months before transitioning to peritoneal dialysis (PD). After a thorough discussion with the patient’s family and genetic studies revealing no pathogenic variants, he was considered an appropriate candidate for renal transplantation.

At 9 years of age, he was admitted for preoperative management ahead of a living donor unrelated kidney transplant. At the time of the procedure, his home medication regimen included levetiracetam and as needed intranasal midazolam

for seizure control; losartan, amlodipine, and isradipine for hypertension; darbepoetin alfa and ferrous sulfate for anemia; cetirizine for allergies; melatonin for insomnia; polyethylene glycol for constipation; and additional metabolic and nutritional support. He took all of his usual daily medications prior to admission except for losartan, which the family was instructed to hold. As part of preoperative care, he was maintained on a low-sodium, low-phosphorus diet and remained *nil per os* for 8 h before surgery. A peripheral intravenous catheter was placed the night prior to the procedure, followed by the first dose of mycophenolate mofetil as part of his pre-transplant immunosuppression regimen. He also underwent overnight PD. On the anesthesia pre-evaluation, the patient’s weight was 29.3 kg, and his vital signs showed a temperature of 36.4 °C, pulse 112 beats/min, blood pressure 109/74 mm Hg, respiratory rate 18 breaths/min, and oxygen saturation of 97% on room air. Cardiac, airway, and respiratory examinations were otherwise unremarkable. Laboratory evaluation was relevant for anemia secondary to ESRD. He was pre-medicated with intravenous midazolam (4 mg) and transported to the operating room (OR).

Routine American Society of Anesthesiologists monitors were applied, and TOF data were obtained using the TetraGraph™ EMG-based monitor (Senzime BV, Uppsala, Sweden), set at a 20-s interval between pulses for TOF-count (TOFC) and TOF-ratio (TOFR). The monitor has a deep blockade mode when the TOFC is 0, allowing for tetanic stimulation with up to 20 single twitch pulses, providing post-tetanic count (PTC) measurements at 2-min intervals. General anesthesia was induced by the administration of propofol (3.5 mg/kg), fentanyl (2 µg/kg), and the inhalation of incremental concentrations of isoflurane in oxygen. Tracheal intubation was facilitated by the administration of rocuronium (1.2 mg/kg) (Table 1). Within 50 - 60 s following the administration of rocuronium, the TOFR was 0%, and oral endotracheal intubation of the patient’s trachea was performed without difficulty using a 5.5-mm cuffed endotracheal tube. There was no patient movement in response to endotracheal intubation. An arterial can-

nula was placed using ultrasound guidance. A bolus dose of levofentanyl (25 mg/kg) was administered. Normothermia was maintained by control of the room temperature and a forced air warming blanket. The intraoperative goal was to maintain $\leq 1/4$ TOFC throughout the procedure. At this point of the procedure, both the TOFC and the PTC were 0. Anesthesia was maintained with isoflurane in air/oxygen and intermittent doses of fentanyl. Forty-five minutes after anesthetic induction, a second dose of rocuronium (0.6 mg/kg) was administered although the PTC measured 1/20, indicating deep NMB. The additional rocuronium bolus dose was administered prior to placement of a triple-lumen central venous catheter in the right internal jugular vein under ultrasound guidance. Prophylaxis to prevent surgical site infections included cefazolin (50 mg/kg) every 3 h. One hour later, the TetraGraph™ showed a TOFC of 1/4, which quickly increased to 2/4 within 10 min, reaching a TOFR of 50% in less than 20 min. A bolus dose of rocuronium (0.6 mg/kg) was administered, followed by the initiation of a rocuronium infusion (0.2 mg/kg/h) to maintain the desired level of NMB.

As part of the perioperative immunosuppressive regimen, the patient received an infusion of methylprednisolone sodium succinate (225 mg in 100 mL of dextrose 5%) over 60 min, followed by an additional 100 mg in 100 mL of dextrose 5% along with acetaminophen (15 mg/kg) and diphenhydramine (1 mg/kg). These medications were administered prior to renal clamp removal. Furosemide (1 mg/kg) and mannitol (0.5 g/kg) were administered at this time to optimize renal perfusion. After graft perfusion was established, anti-thymocyte globulin (37.5 mg in 125 mL of 0.9% sodium chloride) was infused over 6 h. Dopamine (2 - 7 μ g/kg/min) was titrated to maintain hemodynamic stability. One hour after the rocuronium infusion was started, both the TOFC and PTC were consistently 0. The rocuronium infusion rate was decreased to 0.15 mg/kg/h. Fifteen to thirty minutes later, the TOFC was 1. Thirty-five minutes later, toward the procedure's end, the rocuronium infusion was discontinued. Return of the 4/4 TOFC was noted after 15 min, with a TOFR reaching 34%. A dexmedetomidine infusion (0.3 μ g/kg/h) was initiated at this point. Maintenance analgesia was achieved using a multimodal pharmacologic approach including fentanyl, hydromorphone, and acetaminophen. An ultrasound-guided right quadratus lumborum block was placed for postoperative analgesia (15 mL of 0.5% ropivacaine with 1:200,000 epinephrine and 3 mg of preservative-free dexamethasone). With TOFC readings between 2/4 and progressing to 4/4, residual NMB was reversed with a bolus dose of sugammadex (6.5 mg/kg). Within 60 - 90 s, the patient's trachea was extubated when the TOFR was ≥ 0.9 . He was transported to the PICU for further postoperative care.

The intraoperative course was uneventful, and a total volume of 1,000 mL Normosol-R in addition to 250 mL of albumin 5% was administered during the 5 h and 30 min of anesthetic care. Estimated blood loss was 50 mL and total urine output was 390 mL. The postoperative course was uneventful, and the post-transplant renal function rapidly recovered. He was transferred to the inpatient ward on postoperative day 3 and discharged home on postoperative day 10.

Discussion

NMBAs remain an integral part of intraoperative anesthetic care to facilitate endotracheal intubation, prevent intraoperative movement, and provide surgical relaxation. Despite a long history of their use in these clinical scenarios, there remains ongoing discussion regarding the need for objective monitoring of NMB. These concerns may be magnified in the setting of renal failure and other comorbid conditions that alter the normal and expected pharmacokinetic parameters of these agents. Given these concerns, both the American and European Societies of Anesthesiology have recently developed guidelines for monitoring NMB [8, 9]. Both of these societies have provided evidence-based recommendations, with a shared emphasis on the use of quantitative neuromuscular monitoring at the adductor pollicis muscle via ulnar nerve neurostimulation to guide dosing of NMBAs, document adequate reversal at the completion of the surgical procedure, and avoid residual NMB. Residual NMB is considered present when a TOFR below 0.9 is identified at the adductor pollicis muscle. This anatomic site is considered key to confirm adequate recovery. As intraoperative access to this site may be limited and monitoring may be performed at an alternative anatomic location, the ASA Task Force on NMB suggests relocating the monitor to the adductor pollicis site before antagonism of residual NMB, as dosing recommendations are based on responses from this muscle [8]. For amino-steroidal NMBAs such as rocuronium or vecuronium, sugammadex is recommended for reversal of NMB, while neostigmine may be used as an alternative at a minimal depth of blockade. Depth of NMB is defined as deep (PTC ≥ 1 and TOFC 0), moderate (TOFC 1 - 3), shallow (TOFC 4 and TOFR < 0.4), and minimal (TOFR 0.4 to ≤ 0.9).

Based on a significant body of evidence, both task forces highlight the limitations of the qualitative clinical assessment of NMB, including sustained head lift, grip strength, and respiratory measurements. Furthermore, the use of a peripheral nerve stimulator (PNS) is not generally recommended due to poor sensitivity and specificity. While TOFC and PTC can be assessed using a PNS, estimation of twitch strength or clinically significant fade is based on visual or tactile examination. This subjective evaluation is unreliable, especially when the TOFR is > 0.4 , and therefore, cannot be used to confirm adequate recovery (TOFR ≥ 0.9) for tracheal extubation [10]. Despite these limitations, the use of a PNS remains a common practice among providers. Furthermore, the incidence of residual NMB has been shown to be high in adults, with a significant risk of postoperative respiratory complications [11, 12].

Similar practices have been documented in pediatric-aged patients. Although there is a significant risk of residual NMB in pediatric patients with current clinical practices, it is apparent that the incidence of postoperative respiratory compromise may not be as high [13]. Despite the fact that children receiving sugammadex for reversal often show no residual NMB, drug response to both NMBAs and sugammadex is widely variable, particularly in pediatric patients. Therefore, blind or excessive administration of sugammadex does not eliminate the possibility of residual NMB [14]. This variability underscores the limitations of relying on qualitative assessments, such as

PNS and clinical signs, which have previously failed to detect residual NMB in 30% of pediatric patients receiving neostigmine, further supporting the need to transition from qualitative to quantitative NMB monitoring [15].

According to a survey of the Society for Pediatric Anesthesia by Faulk et al, in clinical practice, PNS was the most commonly available qualitative TOF monitoring device, accessible to 80% of respondents, and remained the most frequently used despite being the most prone to error [16]. Notably, the chosen anatomic site for assessment often depended on surgical position in 47% of respondents. Quantitative monitors were available in only 38% of locations, with concerns regarding inaccuracy in neonates and small infants, as well as difficulties with their use, potentially contributing to their limited availability. Overall, the use of neuromuscular monitoring devices is uncommon, especially among providers who received training after the introduction of sugammadex to the United States market in 2015. Anesthesiologists who primarily used sugammadex assessed NMB less routinely (odds ratio (OR): 0.56; 95% confidence interval (CI): 0.34 - 0.90; $P = 0.01$), suggesting that reliance on sugammadex may contribute to this decline [16].

Another challenge in pediatric-aged patients relates to their smaller size and limited space on the volar aspect of the arm, which is usually occupied by intravenous or arterial cannulation. Patient's size presents a challenge for calibration of existing acceleromyography-based monitors, in addition to requiring the target muscle to be seen and move freely, which is a major limitation when the arms are tucked under surgical drapes during laparoscopic or robotic procedures. EMG-based monitors use evoked muscle action potentials rather than relying on physical movement to provide a reading; however, clinical exposure to newer EMG-based TOF monitors such as the TetraGraph™ remains limited in children. In light of the current guidelines, the use of quantitative TOF monitoring has increased in the adult population, but this trend has not been seen yet in pediatric patients.

Recent developments in technology have addressed some of the concerns regarding use of EMG-based TOF monitors in pediatric-aged patients [17-20]. Owusu-Bediako et al evaluated the feasibility and efficacy of using a commercially available EMG-based adult neuromuscular monitor (TetraGraph™, Senzime) with the adult TetraSens™ electrode array in pediatric patients undergoing routine surgeries that required NMBA [17]. Due to the size of the adult sensor, only children weighing over 20 kg were included. The study involved 100 patients (62% male), with the first 50 monitored using the original TetraGraph™ algorithm and the remaining 50 using an updated version that enhanced detection of optimal EMG responses. The monitor recorded TOFR, TOFC, and PTC every 20 s during surgery. Despite being developed for adult use, the TetraGraph™ was shown to be feasible and reliable in children, particularly with the updated software algorithm, supporting its potential as a quantitative monitoring tool. A follow-up prospective study from the same investigators evaluated the feasibility of TOF monitoring using the TetraGraph™ with a new pediatric-specific sensor [18]. The study included 51 patients with a mean age of 3.2 years and a mean weight of 14.2 kg. Notably, 16 patients weighed less than 10 kg, and

25 weighed between 10 and 20 kg. In several instances, the monitored extremity was not easily accessible during surgery, highlighting a key advantage of EMG-based systems, which do not require visual or physical observation of muscle movement. This study confirmed that the TetraGraph™ is feasible even in infants under 10 kg with limited extremity access. Addressing challenges in infants and younger children, particularly size constraints and limited access to the preferred ulnar nerve site, a final study demonstrated the feasibility of monitoring the flexor hallucis brevis muscle (posterior tibial nerve) in the foot [20].

Anecdotal experience from the current case demonstrates yet another scenario where quantitative TOF monitoring may be clinically useful. The rationale for using the TetraGraph™ EMG-based neuromuscular monitor to evaluate rocuronium requirements in this case lies in the unique challenges posed by ESRD and the altered pharmacokinetics and pharmacodynamics of NMBAs in this subset of patients, particularly during renal transplantation when drug elimination may change rapidly. In this setting, NMBAs such as atracurium and cis-atracurium are often preferred because they undergo metabolism in plasma via Hofmann degradation and ester hydrolysis [1, 2]. However, rocuronium is Food and Drug Administration (FDA)-approved for use in pediatric patients and continues to be frequently used, given its rapid onset of action and generally predictable duration. Furthermore, in critically ill patients or longer procedures, as in our case, a continuous rocuronium infusion is sometimes used, offering a stable and sustained NMB [21-24]. Recommended infusion rates are generally 10 - 12 µg/kg/min initially, and 4 - 16 µg/kg/min for maintenance. Although rocuronium is safe to use in patients with renal insufficiency or failure, its effects may be prolonged in such patients.

To ensure appropriate recovery from NMB, sugammadex is often used as a reversal agent. However, sugammadex is highly dependent on renal elimination, with the majority of an intravenous dose (48-86%) excreted unchanged by the kidneys [25-27]. In patients with renal dysfunction, concerns have been raised that sugammadex-NMBAs complexes may accumulate due to a delayed clearance, increasing the risk of recurarization [28-30]. Although clinical trials support the safety of reversal of NMB with sugammadex in patients with renal dysfunction, quantitative TOF monitoring may add additional clinical information not only to guide intraoperative dosing of NMBAs, but to demonstrate effective reversal without recurarization.

Given the above considerations, we adopted an individualized anesthetic strategy, titrating rocuronium based on real-time requirements per quantitative monitoring. This approach helped us mitigate the risks of prolonged NMB or recurarization in the context of CKD, where pharmacokinetics and pharmacodynamics can be unpredictable. In our patient, general anesthesia was induced with propofol, fentanyl, and isoflurane. Tracheal intubation was facilitated with a bolus dose of rocuronium, and neuromuscular function was evaluated using the FDA-approved TetraGraph™ EMG-based monitor and standard PNS. Although a direct analysis of EMG-based TOF versus the PNS to evaluate NMBA requirements was not performed, relevant data comparing the two devices are presented in Table 1. Deep NMB ($\leq 1/4$ TOFC) was maintained through-

out the procedure with additional boluses of rocuronium and a continuous infusion (0.2 mg/kg/h, later decreased to 0.15 mg/kg/h). The TetraGraph™ provided consistent quantitative TOF data, allowing us to monitor the depth and recovery of NMB in real time. This helped us to titrate rocuronium dosing accordingly to maintain the desired level of NMB and reduce the risk of overdosing. This was particularly helpful during periods when the PNS responses were inconsistent or did not seem to correlate with the TetraGraph™ readings. For example, between 09:44 and 10:12, the TetraGraph™ showed a progressive return from 2/4 to 4/4 TOFC twitches, while the PNS showed 0/4 twitches. This disparity highlights the subjective nature of PNS assessments and the importance of quantitative TOF-monitoring to guide clinical decisions. Toward the end of the surgery, the rocuronium infusion was stopped, and residual blockade was reversed with sugammadex, achieving a TOFR ≥ 0.9 within 60 - 90 s. Subsequently, the patient's trachea was extubated, and his postoperative recovery was uneventful.

In summary, we present the use of an EMG-based TOF monitor to evaluate rocuronium requirements and improve safety in a 9-year-old boy with ESRD undergoing renal transplantation. While current clinical guidelines support quantitative TOF monitoring as the gold standard to guide dosing of NMBAs in adults, no such guidelines exist for pediatric patients. Although similar practices have been extrapolated from adult protocols to children, the use of neuromuscular monitoring devices remains uncommon in pediatric anesthesia. However, the presence of CKD and ESRD adds a layer of complexity to anesthetic management, especially in the transplant setting, due to altered pharmacokinetics and pharmacodynamics of NMBAs. Given these concerns, we provide anecdotal experience with the effective clinical use of an EMG-based TOF monitor to guide dosing and reversal of NMB in this clinical setting.

Learning points

Current guidelines recommend the use of quantitative rather than qualitative assessments to guide the administration of NMBAs, confirm adequate recovery, and avoid residual NMB. These guidelines are based on adult studies, and pediatric management is often extrapolated from the adult population due to the lack of pediatric-specific protocols. Despite the risk of residual neuromuscular block, barriers such as limited availability of quantitative TOF monitors in ORs, challenges related to surgical positioning and accessibility, concerns about accuracy due to patient's size, and restricted anatomic space for sensor placement, make quantitative TOF monitoring uncommon in pediatric anesthesia. Novel EMG-based TOF monitors, such as the TetraGraph™, may help overcome some of these barriers. Our case demonstrates how this technology can be useful, especially in challenging circumstances such as CKD in the setting of renal transplantation, guiding intraoperative dosing and ensuring a safe NMB reversal. More robust studies are needed to develop pediatric-specific protocols for neuromuscular monitoring and improve perioperative safety in this vulnerable population.

Acknowledgments

None to declare

Financial Disclosure

None to declare

Conflict of Interest

None to declare

Informed Consent

In accordance with the guidelines of the Institutional Review Board (IRB) of Nationwide Children's Hospital (Columbus, OH), informed consent was obtained for hospital/anesthetic care and the use of deidentified information for publication.

Author Contributions

Preparation of initial, subsequent, and final drafts (EEV, WN); direct patient care, review of final document (GM, SPP); concept, writing, and review of all drafts (JDT).

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

NMBA: neuromuscular blocking agent; NMB: neuromuscular blockade; CKD: chronic kidney disease; AKI: acute kidney injury; TOF: train-of-four; PICU: pediatric intensive care unit; CRRT: continuous renal replacement therapy; HD: hemodialysis; ESRD: end-stage renal disease; TOFC: train-of-four count; TOFR: train-of-four ratio; EMG: electromyography; PTC: post-tetanic count; OR: operating room

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