JPPT | Single Center Retrospective Study

Characterization of Awareness and Depth of Blockade During Neuromuscular Blockade Infusions in Critically Ill Children

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OBJECTIVE The Society of Critical Care Medicine released the first guideline for the prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients but offered conditional recommendations for sedation practices and monitoring during neuromuscular blockade. This study aimed to characterize sedation practices, patient awareness, and depth of blockade with neuromuscular blocking agent (NMBA) infusion administration in a single pediatric and cardiac intensive care unit.

METHODS This retrospective chart review of critically ill pediatric patients queried orders for continuous infusion NMBA. Analgosedation agent(s), dose, and dose changes were assessed, along with depth of blockade monitoring via Train of Four (TOF) and awareness via Richmond Agitation and Sedation Scale (RASS).

RESULTS Thirty-one patients were included, of which 27 (87%) had a documented sedation agent infusing at time of NMBA initiation and 17 patients (54%) were receiving analgesia. The most common agents used were rocuronium (n = 28), dexmedetomidine (n = 23), and morphine (n = 14). RASS scores were captured in all patients; however, 9 patients (29%) had recorded positive scores and 1 patient (3%) never achieved negative scores. TOF was only captured for 11 patients (35%), with majority of the scores being 0 or 4.

CONCLUSIONS Majority of the study population did not receive recommended depth of blockade monitoring via TOF. Similarly, RASS scores were not consistent with deep sedation in half of the patients. The common use of dexmedetomidine as a single sedation agent calls into question the appropriateness of current sedation practices during NMBA continuous infusions.

ABBREVIATIONS ICU, intensive care unit; NMBA, neuromuscular blocking agent; PANDEM, pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients; PICS, post-intensive care syndrome; PICS-p, post-intensive care syndrome in pediatrics; PTSD, posttraumatic stress disorder; RASS, Richmond agitation and sedation scale; TOF, train of four

KEYWORDS analgesia; child; critical care; critical illness; deep sedation; neuromuscular blockade; neuromuscular blocking agents

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Introduction

Neuromuscular blocking agents (NMBAs) are frequently utilized in the intensive care unit (ICU). Given as a continuous infusion, NMBAs facilitate mechanical ventilation, alleviate metabolic demands, and preserve immobility after surgery.[1] In February 2022, the Society of Critical Care Medicine released the first guideline for the prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients (PANDEM). However, it offers conditional recommendations for the selection of analgesia and sedation, degree of awareness, and monitoring during neuromuscular blockade.[2] Specifically, the guidelines *suggest* that "sedation and analgesia should be adequate to prevent awareness prior to and throughout NMBA use" and s*uggest* that "train-of-four (TOF) monitoring be used in concert with clinical assessment to determine depth of neuromuscular blockade."[2]

Past surveys assessed commonly utilized agents for analgosedation and monitoring practices during continuous NMBA infusion. A 2004 national provider survey described midazolam, lorazepam, morphine, and fentanyl were the most utilized agents for analgosedation in the pediatric ICU.[3] Another national survey reported that 63% of participating institutions monitored depth of blockade via peripheral nerve

stimulation.[4] However, few studies have assessed the efficacy of current practices, and none have assessed if practice coincides with the recently released PANDEM guidelines. To address this question, this study aimed to characterize sedation practices, patient awareness, and depth of blockade with continuous NMBA infusion administration in a single pediatric intensive care unit population.

Materials and Methods

A retrospective chart review of patients < 18 years of age admitted to the Kentucky Children's Hospital pediatric cardiothoracic or pediatric ICU was performed. The ICU medication orders were queried from June 2021 through August 2022 for continuous NMBA infusion orders, and patients who had an order placed for continuous NMBA infusion were subsequently included in the study. Patients who did not receive a continuous NMBA infusion or were in the operating room or procedural area during infusion were excluded. The demographic information collected included age and weight. The drug selected, starting, minimum and maximum dose, and number of dose changes were collected for continuous NMBA, analgesia, and sedation infusions. Analgesia and sedation agents were included if they were being administered to the patient at time of continuous NMBA infusion administration. Monitoring endpoint for patient awareness was the Richmond Agitation and Sedation Scale (RASS) collected immediately prior and during continuous NMBA infusion. Depth of neuromuscular blockade was described by TOF values during continuous NMBA infusion. Monitoring of both RASS and TOF at Kentucky Children's Hospital is completed by nursing staff every 4 hours or more frequently if not meeting goals and/or if providing intervention. Continuous variables were assessed via mean and standard deviation if normally distributed or median and interquartile range if not normally distributed. Ordinal variables were assessed by count and frequency. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Kentucky. Data was analyzed in Microsoft Excel (2019). This study received University of Kentucky Institutional Review Board approval.

Results

Baseline Information. A total of 39 patients during the study period were identified but 3 were excluded for not meeting the age requirement and 5 excluded for not having documentation of continuous NMBA infusion administration. Of the remaining 31 patients, the median age was 1 year old (IQR, 0.19–4.0) and the median weight was 9.72 kg (IQR, 4.74–15.2) (Table 1). Rocuronium was selected in 28 patients (90%), 3 (10%) patients received cisatracurium, and none received vecuronium. For rocuronium, the starting dose was 0.55 ± 0.16 mg/kg/hr and the maximum dose was 0.71 ± 0.26 mg/kg/hr. The starting dose of cisatracurium was 0.55 ± 2.83 mcg/kg/min and the maximum dose was 3.91 ± 2.23 mcg/kg/min. Rocuronium had an average of 2.36 dose changes during the infusion, whereas cisatracurium had 2.33 dose changes. The median duration of continuous NMBA infusion was 35.88 hours (IQR, 17.03–58.95).

Analgosedation Practices. At time of continuous NMBA infusion administration, 27 patients (87%) had a documented sedative agent infusion. The most common sedative agent was dexmedetomidine (n = 23) and the median starting dose was 1.09 ± 0.43 mcg/kg/hr and maximum dose was 1.31 ± 0.34 mcg/kg/hr. Other agents utilized included midazolam (n = 5), propofol (n = 6), ketamine (n = 2), and pentobarbital (n = 1) (Table 2). Prior to continuous NMBA infusion, 17 patients (54%) were receiving continuous analgesia infusion. Morphine (n = 14) was the most common infused analgesic, followed by fentanyl (n = 2) and hydromorphone (n = 1) (Table 2). Eight of the 27 (30%) patients were receiving 2 sedative agents and 1 of the 27 (3%) patients had 3 sedative agents. The frequency of different analgosedation combinations were noted, with the use of dexmedetomidine and an opioid being the most common combination (n = 12) (Table 3). Four patients had no concurrent sedation infusion documented, and only 1 of whom had an analgesic infusion at time of NMBA initiation. The analgosedation agents that had the highest mean number of dose changes to achieve desired level of sedation were propofol (7.33), hydromorphone (6), followed by dexmedetomidine (2.83) and morphine (2.83) (Table 2).

Table 1. Patient Baseline Information (N = 31)

	Results
Age, median (IQR), yr	1 (0.19–4.0)
Weight, median (IQR), kg	9.72 (4.73–15.2)
NMBA selection, n (%)	
Cisatracurium	3 (10%)
Rocuronium	28 (90%)
Vecuronium	0 (0%)
Duration of NMBA, median (IQR), hr	35.88 (17.03–58.95)
NMBA start, n (%)	
Day shift (07:00–18:59)	18 (58%)
Night shift (19:00–06:59)	13 (42%)
NMBA stop, n (%)	
Day shift (07:00–18:59)	25 (81%)
Night shift (19:00–06:59)	6 (19%)
Time from previous RASS to start of NMBA infusion, median (IQR), hours	0.98 (0.6–2.26)

IQR, interquartile range; NMBA, neuromuscular blocking agent

Table 2. Sedation and Analgesic Drug Average Doses and Dose Changes

Sedative Agent	**Start Dose**	**Min Dose**	**Max Dose**	**Dose Changes**
Dexmedetomidine, mean (SD), mcg/kg/hr	1.09 (0.43)	0.64 (0.54)	1.31 (0.34)	2.83 (2.44)
Ketamine, mean (SD), mg/kg/hr	2 (1.41)	1.5 (0.71)	2.5 (0.71)	1.5 (0.71)
Midazolam, mean (SD), mg/kg/hr	0.51 (0.85)	0.43 (0.88)	0.73 (1.28)	0.8 (0.84)
Propofol, mean (SD), mcg/kg/min	85 (23.45)	20.83 (40.05)	139.18 (84.28)	7.33 (6.02)
Analgesic Agent	**Start Dose**	**Min Dose**	**Max Dose**	**Dose Changes**
Fentanyl, mean (SD), mcg/kg/hr	2.5 (2.12)	2.5 (2.12)	5 (4.24)	1 (0)
Hydromorphone, mean (SD), mcg/kg/hr	0.7	0.35	0.9	6
Morphine, mean (SD), mcg/kg/hr	83.25 (52.1)	59.04 (58.4)	126.89 (79.16)	2.83 (3.24)

Level of Awareness. Prior to continuous NMBA initiation, RASS scores were collected in 27 patients (87%) with an average time from score to NMBA initiation of 0.98 (IQR 0.6-2.26) hours. The goal RASS of −4 to −5 to signify deep sedation prior to continuous NMBA infusion initiation was achieved in 12 of 27 patients (44%). However, 4 patients (13%) had no scores charted prior to continuous NMBA infusion initiation and 15 of 27 patients (56%) did not achieve deep sedation before receiving neuromuscular blockade. RASS scores were recorded in all patients (n = 31) during continuous NMBA infusion. The goal RASS of −4 to −5 was achieved at least once during continuous NMBA infusion in 30 patients (97%). At some point during the continuous NMBA infusion, 17 (55%) patients had scores not consistent with deep sedation, 9 patients (29%) had at least 1 positive score recorded, and a single patient never achieved a negative RASS (Figure). A total of 11 patients (35%) had all scores consistent with deep sedation, and the median percent of documented RASS consistent with deep sedation for all patients was 83% (IQR, 65%–100%).

Depth of Blockade. Peripheral nerve stimulation with TOF monitoring was captured in 11 patients (35%), but only 2 (18%) were maintained in the goal TOF range of 1 to 2 twitches out of 4 twitches. Eight patients (73%) had a score of 4/4 twitches, consistent with inadequate neuromuscular blockade. Eight of the 11 patients (73%) had at least 1 score of 0/4 twitches during continuous NMBA infusion, and a single patient only had scores of 0/4 twitches reported during the entire continuous NMBA infusion, which is consistent with excessive neuromuscular blockade.

Discussion

The PANDEM guidelines provide guidance for pediatric critical care practitioners by suggesting the use of analgosedation to prevent awareness prior and throughout NMBA use and recommend utilization of TOF monitoring with clinical assessment to monitor depth of blockade.[2] This study aimed to examine local application of these guideline recommendations.

Dexmedetomidine is conditionally recommended by the PANDEM guidelines as the primary sedative agent for critically ill children undergoing mechanical ventilation and strongly recommended as primary sedation for post-operative cardiac surgery patients.[2] Dexmedetomidine is a centrally acting alpha-2 agonist that preserves the respiratory drive while providing "arousable and cooperative" sedation, anxiolysis, and some analgesic properties.[5] It has increased in popularity of use because of these properties, as well as in prevention of ICU delirium in pediatric and adult populations alike.[2,6] Dexmedetomidine appears to be a favorable sedative for many scenarios, but may not be the best choice in situations involving NMBA with this level of sedation. In fact, dexmedetomidine is featured as the first-line sedative agent in our pediatric ICU and pediatric cardiac ICU analgosedation guideline, with pain management being initiated as morphine IV boluses, and then escalating to a continuous morphine infusion if more than 3 boluses are received in 3 hours. However, this institutional guideline does not offer an analgosedation approach to the neuromuscularly blocked patient.

The selection of the most appropriate sedative agent for continuous NMBA infusion should be one that is "adequate to prevent awareness prior to and throughout NMBA use" per the PANDEM guidelines.[2] In 1 pediatric single center trial, intubated children were randomly assigned to receive either midazolam or dexmedetomidine continuous infusion for 24 hours with as needed morphine injection. Patients receiving 0.25 mcg/kg/hr of dexmedetomidine had a similar level of sedation to that of midazolam 0.22 mg/kg/hr. However, the mean Ramsey sedation scale attained in this study was approximately 3 for all groups, which signifies response to command, light touch, or tone of voice, which is not consistent with lack of awareness and deep sedation necessary for NMBA.[7] In the present study, the majority of patients received dexmedetomidine (74%) as sedative agent, whereas 16% patients received a midazolam infusion. Our study RASS scores were not consistent with deep sedation during the entirety of the NMBA infusion. Increased use of dexmedetomidine over midazolam and other amnestic agents likely contributed to not achieving the desired level of sedation and not ensuring decreased awareness during NMBA infusions. This conclusion is further defended by the 2018 SCCM publication Clinical Practice Guidelines for Sustained

Table 3. Combinations of Analgosedation Utilized*

Patient	DEX	MDZ	KET	PPF	PTB	MOR	FEN	HYD
1	■	■		■				
3		■		■				
4	■					■		
5	■					■		
7	■			■		■		
8	■							
9	■	■				■		
12				■	■			
13	■							
14	■							
15	■			■				■
16	■	■						
18			■	■				
19	■						■	
20	■							
21	■					■		
22	■					■		
23								
24	■					■		
25	■					■		
26								
27			■					
28	■					■		
29	■					■		
30	■							
31						■		
32								
33	■					■		
34	■	■					■	
35	■					■		
36	■					■		

Combination	N (%)
DEX alone	5 (16.1)
DEX and OPD	12 (38.7)
DEX and MDZ	1 (3.2)
DEX, MDZ, and PPF	1 (3.2)

(Table cont. on page 372)

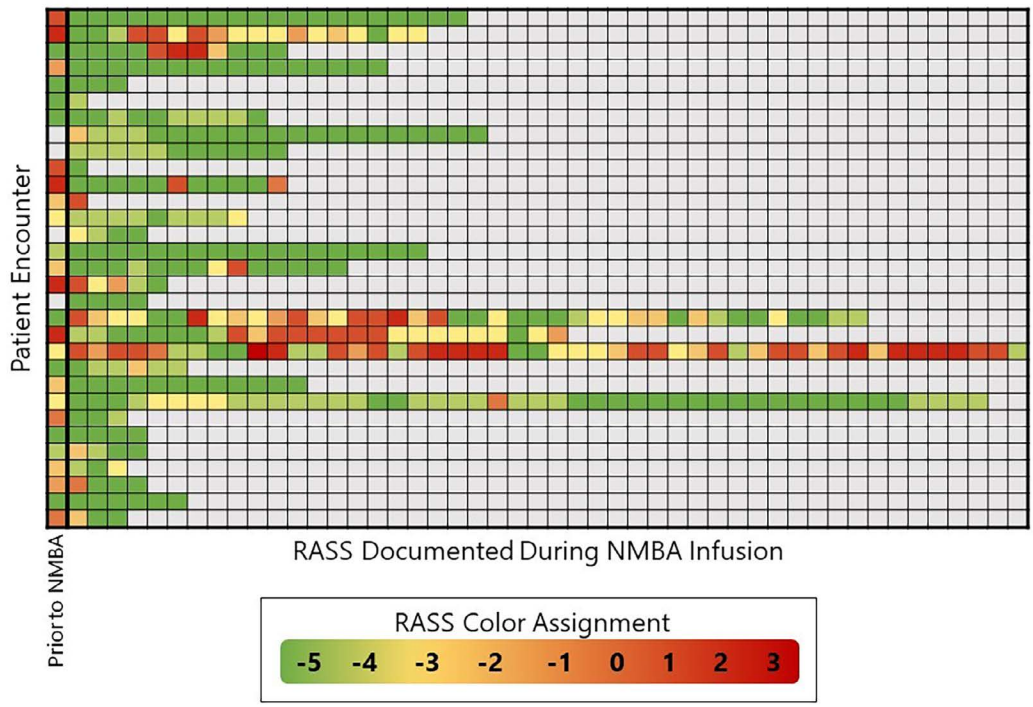
Table 3. Combinations of Analgosedation Utilized* *(cont.)*

Combination	N (%)
DEX, MDZ, and OPD	2 (6.5)
DEX, PPF, and OPD	2 (6.5)
PPF and MDZ	1 (3.2)
PPF and KET	1 (3.2)
PPF and PTB	1 (3.2)
KET alone	1 (3.2)
OPD alone	1 (3.2)
None	3 (9.7)

DEX, dexmedetomidine; FEN, fentanyl; HYD, hydromorphone; KET, ketamine; MDZ, midazolam; MOR, morphine; OPD, opioid; PPF, propofol; PTB, pentobarbital. Total of 31 study patients.

* Blue shaded areas represent patient receipt of medication.

Figure. Heat map of RASS immediately prior and during NMBA infusion.



NMBA, neuromuscular blocking agent; RASS, Richmond Agitation and Sedation Scale

Neuromuscular Blockade in the Adult Critically Ill Patient which specifically states that "dexmedetomidine should not be used when deep sedation (with or without neuromuscular blockade) is required."[6]

A few retrospective studies have assessed awareness during mechanical ventilation and neuromuscular blockade. Risk factors for awareness have been found to include underdosing of sedatives and a lack of protocolized monitoring for depth of sedation. At our institution for a patient receiving a sedative infusion, the expectation is to assess RASS every 4 hours, and more frequently if there are changes in clinical status. This study revealed that 39% of our patients achieved the desired RASS at least 1 hour before NMBA was administered, but left 48% of patients in a state of awareness and 13% had no RASS documented

prior to NMBA administration so it is unknown if lack of awareness was achieved. Absence of awareness during NMBA administration is necessary as it prevents patients from experiencing psychological sequalae, including posttraumatic stress disorder (PTSD) and depression.[8] Three common experiences that patients remember include being between life and death, loss of control, and almost dying.[9] Another study found that children who were inadequately sedated endorsed feeling fear, anxiety, and sleepiness while being neuromuscularly blocked.[10] In the present study, 55% of patients were found to have RASS scores not consistent with deep sedation during NMBA infusion. Therefore, majority of the patients in this study were at risk for developing psychological sequalae and thus increased risk of post-intensive care syndrome (PICS). The sequelae of PICS in pediatrics (PICS-p) influences child and family recovery outside of the ICU.[11] The impact of PICS-p is classified based on symptoms experienced, which include physical, cognitive, emotional, and social. Studies have reviewed the incidence of these symptoms and found that 36% of children experience physical symptoms, 3.4% experience cognitive, 66% emotional, and 70% social.[11] The development of PICS has been reduced by decreasing deep sedation and prolonged immobilization in adult ICU survivors.[12] However, deep sedation is required during neuromuscular blockade thus eliminating one PICS prevention strategy.

The PANDEM guidelines suggest the use of "TOF monitoring be used in concert with clinical assessment to determine depth of neuromuscular blockade."[2] In our unit, peripheral nerve stimulation with TOF is to be captured at baseline before NMBA is introduced, and then assessed hourly until at goal, and every 4 hours once TOF goal is achieved. However in our unit, we found this baseline assessment is not routinely captured, which limits further testing of depth of neuromuscular blockade during continuous infusion. This low application of TOF monitoring in our cohort (35% of patients) may have been due to precipitous changes in clinical status necessitating NMBA or could have been due to any number of contributing user, patient, and technical factors that adversely affect TOF reliability (i.e., unfamiliarity in using TOF, younger age, peripheral edema, or diaphoresis). Additionally, due to the retrospective nature of our study, the clinical assessment of depth of blockade could not be easily obtained from documentation to help inform our unit practice. The frequency of TOF monitoring in our study is consistent with that found in other studies, such as the less than the 63% reported by Foster and colleagues.[4] The reasoning for non-use of TOF in the Foster study was unavailable equipment, lack of training, and lack of evidence supporting the use of peripheral nerve stimulation for monitoring depth of blockade.[4] Our study did not collect reasoning for non-adherence to TOF monitoring, but it would be valuable information to collect for future studies.

While this study did have interesting findings, one major limitation is the retrospective nature. As such, data collected are based on observational data derived from nursing documentation for drug administration, level of sedation, and depth of neuromuscular blockade. The entire study period took place during local surges of COVID-19 Delta and Omicron variant, which was a challenging time for the health care workforce to manage patient volume and acuity. The temporality of the charted documentation with what is occurring at the bedside is often not precise, especially in an unstable, critically ill patient, which may explain some of our unfavorable results. Additionally, a multimodal approach to assessment of depth of sedation with neuromuscular blockade has been suggested (i.e., electroencephalogram-based monitoring), but currently our standard of practice is RASS, TOF, and clinical assessment.[2] TOF was not consistently utilized, which is a practice that has been difficult to reliably apply to all NMBA infusions in our unit. Additionally, the study only captured sedation and analgesic infusions that were already infusing at time of NMBA administration. Not included were agents started during NMBA infusion or the use of as needed analgosedation agents before or during NMBA infusion.

The results of this study show areas of improvement in our current practice of agent selection, depth of awareness and blockade monitoring in order to align with PANDEM guideline recommendations. Furthermore, this study provides a practical perspective of pediatric analgosedation practices with NMBA, and the current gaps in literature that plague putting analgosedation guidelines into practice. This study suggests that dexmedetomidine does not provide the appropriate level of sedation and loss of awareness for NMBA, and that alternative sedative agents should be utilized to decrease patient awareness.

Conclusion

This study afforded a closer look into analgosedation practices with continuous NMBA infusions in 1 pediatric hospital. In this study, rocuronium was the most frequently used continuous NMBA infusion. Morphine was the agent of choice for analgesia and dexmedetomidine the most common selection for sedation. Dexmedetomidine is a sedative agent without amnestic properties and well known to not cause deep sedation. Therefore, dexmedetomidine use as a single sedative agent to decrease patient awareness during continuous neuromuscular blockade infusion needs to be addressed and alternative sedatives offered. Unfortunately, the PANDEM guidelines do not offer guidance on the specific agent(s) to use to decrease patient awareness during continuous NMBA infusion; further investigation is required to determine the appropriate

analgosedation regimen during continuous NMBA infusion. Furthermore, RASS scores were not consistent with deep sedation during continuous NMBA infusion in half of the patients, likely a reflection of using dexmedetomidine as the sedative agent. This study also found that current practice does not follows PANDEM guidance regarding depth of neuromuscular blockade monitoring via TOF. Internal measures will need to be taken to refine unit guidelines to improve the practice of decreasing awareness during neuromuscular blockade for critically ill children.

Article Information

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