Survey of the Current Use of Dexmedetomidine and Management of Withdrawal Symptoms in Critically Ill Children

R. Zachary Thompson, PharmD; Brian M. Gardner, PharmD; Elizabeth B. Autry, PharmD; Scottie B. Day, MD; and Ashwin S. Krishna, MD

OBJECTIVES Dexmedetomidine use for sedation in the pediatric intensive care units (PICUs) has increased since its initial US Food and Drug Administration (FDA) approval in adults. However, there is limited evidence to direct providers regarding current usage, dosing, and monitoring for withdrawal symptoms in pediatric patients. This study sought to determine the utilization of dexmedetomidine and management of dexmedetomidine withdrawal symptoms among PICU physicians.

METHODS A questionnaire survey was distributed to all members of the American Academy of Pediatrics Section on Critical Care. It assessed the practice site demographics, indication, dosing, and duration of dexmedetomidine infusion, unit protocol, and strategies for management of dexmedetomidine withdrawal.

RESULTS A total of 147 surveys (21.1%) were returned and analyzed. The reported uses for dexmedetomidine were as a primary sedative (59.9%), adjunctive agent for sedation (82.3%), and adjunctive agent to assist weaning sedation (62.6%) or from mechanical ventilation (70.1%). One hundred twenty-nine respondents (87.8%) had concerns over dexmedetomidine withdrawal, with 59 respondents becoming concerned after 120 hours of infusion (45.7%). Most respondents reported managing dexmedetomidine withdrawal symptoms via a regimented wean and initiation of clonidine (81%). Units with >1000 admissions per year were more likely to have a protocol related to dexmedetomidine use ($p = 0.021$). Units with >1000 admissions per year reported using clonidine for withdrawal at a higher rate, whereas units with ≤ 1000 admissions per year used a systematic wean of dexmedetomidine ($p = 0.014$).

CONCLUSIONS Dexmedetomidine use in the PICU is varied among pediatric intensive care physicians. Intensivists have withdrawal concerns after dexmedetomidine discontinuation, and the primary management of this withdrawal phenomenon is the initiation of clonidine with a regimented dexmedetomidine wean.

ABBREVIATIONS AAP-SOCC, American Academy of Pediatrics Section on Critical Care; FDA, US Food and Drug Administration; PICU, pediatric intensive care unit; WAT-1, Withdrawal Assessment Tool-1

KEYWORDS critical care; dexmedetomidine; pediatric; sedation; withdrawal

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Introduction

Ensuring the safety and comfort of critically ill infants and children supported by mechanical ventilation is integral to the practice of pediatric critical care.¹ The use of dexmedetomidine, a selective α_2 -adrenoreceptor agonist, has increased in pediatric critical care as an adjunct to traditional sedation.² The therapeutic effects of dexmedetomidine are via reduction of norepinephrine in the sympathetic nerve endings in the central and peripheral nervous systems.³ This mechanism of action results in sedation, anxiolysis, and analgesia with little effects on the respiratory drive of a patient.⁴ There is an increasing amount of safety data and comfort with dexmedetomidine use in the pediatric intensive care

unit (PICU), yet it has previously been shown that sedation practices among pediatric intensivists vary across different practice environments.⁵

Despite increasing use in the pediatric population, dexmedetomidine only has US Food and Drug Administration (FDA) approval for adult patients for up to 24 hours⁶ and at doses of 0.2 to 0.7 mcg/kg/hr. Safe dosing of up to 2 mcg/kg/hr has been described in the pediatric population to assist and facilitate with procedural sedation.⁷ Most data on the use of dexmedetomidine in the pediatric population limit its use to 72 hours⁸; however, reports have been detailed with infusions of greater than 120 hours.²

The traditional pharmacologic regimen for sedation in the PICU has consisted of opioids and benzodiaz-

epines. Tolerance and dependency are known to occur with the use of these agents.^{9,10} Abrupt discontinuation of opioids and benzodiazepines has been known to lead to withdrawal symptoms in children. Dexmedetomidine was not observed to cause a withdrawal syndrome when first used in the pediatric critical care population; however, with increased use and duration of infusions, withdrawal symptoms have been described.^{2,11} The most common withdrawal symptoms of dexmedetomidine infusions described in the literature are rebound hypertension and tachycardia, increased agitation, and tremors.^{2,12} A slow methodical taper of a prolonged dexmedetomidine infusion and initiation of an alternative α_2 -agonist, such as clonidine, have both been used as strategies to manage withdrawal symptoms.^{13,14}

Clonidine is a centrally acting α_2 -adrenoreceptor agonist and is similar in structure to dexmedetomidine. Clonidine has an α_2 to α_1 receptor specificity of 200:1, whereas dexmedetomidine's ratio is 1600:1, and clonidine's half-life is substantially longer than dexmedetomidine's at 12 to 24 hours versus 2 to 3 hours.³ Lardieri et al¹³ described the use of clonidine in treating patients with withdrawal symptoms after discontinuation of dexmedetomidine. This study showed a trend toward lower Withdrawal Assessment Tool-1 (WAT-1) scores during the initial 24 hours and significantly lower heart rates in the treatment group.

Although the available published pediatric data related to dexmedetomidine use for sedation within the PICU suggest safety and efficacy, there are no guidelines to direct PICU practitioners regarding defined indications, optimal dosing, and duration of therapy. Furthermore, no guidelines exist regarding the identification and management of dexmedetomidine withdrawal. Knowing this background information, the aim of this study is to determine a broad view of the current use of dexmedetomidine as well as identification and management of dexmedetomidine withdrawal by practitioners within the PICU.

Materials and Methods

Participants. The institutional review board at the University of Kentucky approved the survey and the study with waived informed consent. The study sample included all members of the American Academy of Pediatrics Section on Critical Care (AAP-SOCC). At the time of the survey, the AAP-SOCC had participation of 695 members, including 11 international members.

Survey. One questionnaire was sent out via email and participants were instructed to provide 1 response per person. Responses were made via an electronic data capture tool (REDCap, Vanderbilt University, Nashville, TN) and were automatically cataloged in the database.¹⁵

Questionnaire. The questionnaire was developed by the research team, which included a pediatric pharmacy resident, pediatric clinical pharmacy specialists, and

Table 1. Questionnaire Respondent Demographics (N = 147)

Characteristics	Results
Admissions per year, n (%)	
<300	7 (5)
301–600	22 (15)
601–1000	26 (18)
1001–1500	46 (31)
>1501	46 (31)
Type of unit, n (%)	
Medical and surgical ICU	71 (48)
Cardiovascular ICU	7 (5)
Mixed medical/surgical and cardiovascular ICU	69 (47)
Median number of beds, median (range)	
Medical and surgical ICU	16 (4–55)
Cardiovascular ICU	22 (6–29)
Mixed medical/surgical and cardiovascular ICU	24 (11–72)
Dedicated cardiology beds	6 (0–32)

ICU, intensive care unit

pediatric intensive care physicians (RZT). The 64-field survey included skip logic allowing physicians to provide answers to only necessary questions based on previous responses. The questionnaire assessed the practice site demographics, indication, dosing, and duration of dexmedetomidine infusion, unit protocol, concern for withdrawal and symptoms observed, and description of dexmedetomidine withdrawal strategies. Management of withdrawal included weaning of dexmedetomidine infusion, dosing and route of clonidine, monitoring parameters and durations of clonidine weans. Description of units was divided into 4 categories on the basis of admissions per year from a national survey of pediatric critical care resources in the United States.¹⁶

Statistical Analysis. One set of data was collected from each respondent. Descriptive statistics were used to analyze demographics and responses. Chi-square testing was performed to determine the differences among units with >1000 admissions per year versus units with ≤ 1000 units per year and a p value of <0.05 was deemed to be statistically significant.

Results

Demographics. A total of 153 questionnaires were returned with 3 responses left incomplete and 3 responses excluded owing to extreme outlying values. A total of 147 questionnaires (21.1%) were included for analysis. Demographics were based on type and number of beds in the intensive care unit and admissions per year (Table 1).

Table 2. Dexmedetomidine Use (N = 147)

Characteristic	Results
Indication, n (%)	
Primary sedative	88 (59.9)
Adjunctive sedative in patients requiring large doses of other sedative medications	121 (82.3)
Adjunctive sedative in patients requiring weaning from other sedative medications	92 (62.6)
Adjunctive sedative to facilitate weaning from mechanical ventilation	103 (70.1)
Typical duration of therapy*, n (%)	
<24 hr	1 (0.9)
24–48 hr	25 (22.1)
48–120 hr	69 (61.1)
>120 hr	18 (15.9)
Starting dose, median (range)	0.4 mcg/kg/hr (0.03–1 mcg/kg/hr)
Maximum dose, median (range)	1.5 mcg/kg/hr (0.7–5 mcg/kg/hr)

* Included if no institutional protocol is available (n = 113).

Dexmedetomidine Use. Regarding the indication for dexmedetomidine most respondents answered that dexmedetomidine was used as an adjunct sedative in the presence of large doses of concomitant sedatives (82.3%). Sixty percent of respondents reported using dexmedetomidine as a primary sedative in their practice. The median starting dose was 0.4 mcg/kg/hr and the median maximum dose was 1.5 mcg/kg/hr. Also, only 9 respondents reported to limiting their dexmedetomidine duration in their practice (Table 2).

Institutional Protocols. Thirty-four respondents reported having an institutional protocol related to dexmedetomidine infusions. None of the respondents reported limitation of less than 24 hours for infusion duration and the dosing range was similar to those reported in practice (0.4–1.5 mcg/kg/hr).

Withdrawal Occurrence. Eighty-eight percent of respondents reported having concerns for withdrawal symptoms developing with dexmedetomidine discontinuation, while 18 respondents (12%) reported no concerns in their practice regarding dexmedetomidine withdrawal. Withdrawal symptoms were most commonly suspected with infusions lasting longer than 120 hours (Figure). The most common symptoms attributed to dexmedetomidine withdrawal were irritability (96%), tachycardia (89%), and hypertension (88%).

Withdrawal Management. One hundred four respondents (81%) reported using a regimented wean of dexmedetomidine with concomitant initiation of clonidine for management of withdrawal. Physicians in intensive care units with more than 1000 admissions per year were more likely to answer that they initiated clonidine in conjunction with a regimented wean of dexmedetomidine (78.3% versus 56.4%) ($p = 0.014$). Although the clonidine dosing was variable (Table 3), enteral clonidine at a starting dose of 1 mcg/kg at an

interval of every 6 hours was the most common regimen reported. Twenty-nine percent of physicians reported using transdermal clonidine patches for management of withdrawal. Owing to the nature of this survey, we were unable to assess the administration techniques of transdermal clonidine. Most patches were changed every 7 days (56%); however, 25% of respondents reported changing every 3 days and 19% reported changing every 5 days. When asked about monitoring of withdrawal symptoms, 74% of physicians reported using WAT-1 scores.¹⁷

Discussion

PICU providers rely upon clinical practice experiences owing to the lack of strong randomized clinical trials for many medications used. Dexmedetomidine's use has increased in recent years owing to its minimal effects on respiratory drive and the potential detrimental effects of other sedative medications.¹⁸ The results of this questionnaire provide the first description of the utilization of dexmedetomidine and management of withdrawal symptoms in PICUs across the broad spectrum of practice models and locations represented by the AAP-SOCC.

In our study 60% of respondents stated that they used dexmedetomidine as a primary sedative in their practice. These data suggest that physicians are becoming more comfortable with dexmedetomidine and are using it as a primary, first-line sedative agent. Whalen et al² described the long-term use and safety of dexmedetomidine; however, their primary indication for dexmedetomidine use was secondary to increased benzodiazepine and opioid use due to development of tolerance over time. This difference may represent a recent change in practice due to increasing knowledge regarding the detrimental effects of benzodiazepine in-

Figure. Duration of dexmedetomidine when withdrawal considered.

*12 hr, 48 hr

fusions.¹⁸ The respondents in the current study also use dexmedetomidine at larger doses and for longer durations than in the FDA labeling, which further suggests an increased comfort with using dexmedetomidine in pediatric critical care practice.⁶

Owing to the higher cost of dexmedetomidine compared to traditional sedative options, institutions may limit the prescription to specific patient populations. In our study, most institutions did not report protocols to manage or assist physicians with dexmedetomidine management. In institutions with more than 1000 admissions per year there was a trend toward having dexmedetomidine protocols. This may represent a consensus among numerous pediatric intensivists to direct and standardize sedation practices. The institutional protocols also detailed larger doses and longer durations than in the FDA labeling, again suggesting increased comfort among pediatric intensivists.

Iatrogenic withdrawal from sedative medications is a known phenomenon in the PICU.¹⁰ Dexmedetomidine's use has evolved over time and with physicians expanding the durations of infusions to longer time periods, withdrawal symptoms have been described in the literature.^{12,13} The respondents in our study most commonly expressed concern about withdrawal after infusions beyond approximately 120 hours of duration. This timeframe is consistent with the proposed onset of withdrawal associated with prolonged opioid and benzodiazepine use. Management of iatrogenic withdrawal from opioids and benzodiazepines is accomplished via slow decreases of intravenous drips, initiation of enteral medications, or a combination of both. Commonly methadone, morphine, lorazepam, and diazepam are used to decrease opioid and benzodiazepine drips and are weaned off over time.¹⁹

Clonidine has been used to assist with dexmedetomidine withdrawal,¹³ and the respondents of our study identified a regimented wean of the infusion and ini-

tiation of clonidine as the primary means of managing symptoms. There is no known dose equivalent of clonidine and dexmedetomidine; however, the respondents of our study most commonly used a starting enteral dose of 1 mcg/kg every 6 hours. Regarding transdermal use of clonidine, we were unable to evaluate administration techniques regarding doses smaller than whole patches or frequency of patch changes. There are limited data regarding administration of clonidine patches in pediatric patients.²⁰ In the authors' institution clonidine patches are changed every 5 days owing to historical experiences with patches dislodging secondary to sweating and impaired adhesive.

WAT-1 is commonly used for monitoring of withdrawal symptoms from benzodiazepines and opioid infusions in the PICU.¹⁷ This scoring system has not been validated with symptoms of dexmedetomidine withdrawal; however, some aspects of dexmedetomidine withdrawal may be encompassed within the WAT-1 score. The WAT-1 score includes patient assessment of tremor and agitation, which has been described in patients with withdrawal symptoms from dexmedetomidine.²

This survey is intended to provide a description of the current practice surrounding dexmedetomidine in PICUs. The main limitation of this study is the questionnaire design, which is a collection of interest to the investigators and may impose bias in respondents. Secondly, the overall response rate for this survey was significantly lower than for previous studies detailing other practice patterns in PICUs.⁵ This may be in part due to the list-serve we used to distribute the survey. This survey was distributed to a large group of physicians that are part of the AAP-SOCC and is made up of attending physicians, residents, fellows, and retired members. The survey was directed at currently practicing attending physicians but we are unable to verify the respondent's current practice.

Overall, an increasing number of pediatric intensive

Table 3. Clonidine Use*

Characteristic	Result, n (%)
Route (n = 110)	
Enteral	78 (71)
Transdermal	32 (29)
Enteral dose (n = 78)	
1 mcg/kg	48 (62)
2 mcg/kg	18 (23)
3 mcg/kg	9 (12)
Other	3 (4)
Enteral frequency (n = 78)	
Every 4 hr	6 (8)
Every 6 hr	43 (55)
Every 8 hr	24 (31)
Every 12 hr	5 (6)
Transdermal dose per 24 hr (n = 32)	
0.05 mg	4 (13)
0.075 mg	1 (3)
0.1 mg	19 (59)
0.2 mg	1 (3)
Other	7 (22)
Transdermal change frequency (n = 32)	
Every 3 days	8 (25)
Every 5 days	6 (19)
Every 7 days	18 (56)

* Initial dosing.

care physicians are using dexmedetomidine as a primary sedative, using larger doses and longer durations than described in the package labeling. A small percentage of respondents reported protocols regarding dexmedetomidine use or regulate their practice in the intensive care unit. Lastly, dexmedetomidine withdrawal is a concern among many pediatric intensivists with the primary management being a regimented wean along with the initiation of an enteral alpha-2 agonist.

From the results of our study, we believe that dexmedetomidine can be used as a primary sedative agent in a PICU setting and further studies may need to be conducted regarding the dosing, indications, and contraindications. Also, larger doses and longer durations of infusions suggest that clinicians need to be equipped at management of withdrawal from dexmedetomidine using clonidine, infusion weans, or both. Further research is needed to clarify dexmedetomidine's ideal indications, optimal dosing, and withdrawal management within the PICU.

ARTICLE INFORMATION

Affiliations Nationwide Children's Hospital Department of Pharmacy (RZT), Columbus, Ohio; University of Kentucky Children's Hospital Pharmacy Services (BMG, EBA), Lexington, Kentucky; University of Kentucky College of Pharmacy (BMG, EBA), Lexington, Kentucky; Department of Pediatrics (SBD, ASK), University of Kentucky College of Medicine, Lexington, Kentucky

Correspondence Ashwin S. Krishna, MD;
ashwin.krishna@uky.edu

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