Evaluating the Transition From Dexmedetomidine to Clonidine for the Prevention of Withdrawal in Critically Ill Pediatric Patients

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OBJECTIVES To evaluate clonidine for preventing withdrawal from dexmedetomidine infusions and describe the incidence of withdrawal symptoms and adverse cardiovascular effects in critically ill pediatric patients.

METHODS Retrospective, descriptive study of patients in Advocate Children's Hospital-Park Ridge PICU who received dexmedetomidine infusion for ≥ 72 hours, followed by clonidine for ≥ 48 hours, between January 1, 2015, and August 31, 2017.

RESULTS Thirty-eight patients (median age 4.3 years; IQR, 2–11.5) received 39 dexmedetomidine courses. The median duration of dexmedetomidine exposure was 7.6 days (IQR, 5–11.5) at an average dose of 1 mcg/kg/hr. The median dose of clonidine at initiation was 8.3 mcg/kg/day (for <50 kg) and 4.1 mcg/kg/day (for ≥ 50 kg). The most common oral administration frequency was every 8 hours. Dexmedetomidine infusions for 7 days or longer and a higher dexmedetomidine dose 24 hours prior to clonidine transition both correlated with increased initial clonidine doses. Fourteen patients (37%) had at least 1 WAT-1 score of ≥ 3 during the transition between dexmedetomidine and clonidine, with 7 (18%) requiring an increase in sedation. Adverse cardiovascular events were possibly attributable to dexmedetomidine and/or clonidine in 4 patients.

CONCLUSIONS Patients receiving prolonged infusions of dexmedetomidine may transition to clonidine to help prevent withdrawal symptoms. Duration of dexmedetomidine infusion of 7 days or longer and higher average dexmedetomidine dose 24 hours prior to the transition are important considerations when determining the initial clonidine dose. Transition from dexmedetomidine to clonidine was found to be safe and efficacious in our patients, with minimal adverse effects.

ABBREVIATIONS FDA, US Food and Drug Administration; IQR, interquartile range; PICU, pediatric intensive care unit; WAT-1, Withdrawal Assessment Tool-1

KEYWORDS clonidine; critically ill; dexmedetomidine; pediatric; withdrawal

J Pediatr Pharmacol Ther 2020;25(2):104–110

DOI: 10.5863/1551-6776-25.2.104

Introduction

Critically ill pediatric patients commonly need sedation for a variety of reasons, including intubation for mechanical ventilation, agitation, and comfort.¹ Benzodiazepines and opioids are administered as a continuous infusion to provide sedation, but are associated with adverse effects such as respiratory depression, hemodynamic instability, and potential withdrawal.

Dexmedetomidine is an α_2 -adrenoreceptor agonist, FDA approved for sedation of intubated and mechanically ventilated adults in the intensive care unit not to exceed 24 hours.² There is no FDA-approved indication in pediatrics, but dexmedetomidine is increasingly being used off-label for sedation in PICUs owing to its advantages as a short-acting, rapid-onset, intravenous continuous infusion (doses ranging from 0.1 to 2.5 mcg/kg/hr).³ While it has less effect on respiratory function and delirium than benzodiazepines and opioids, dex-

medetomidine can cause cardiovascular side effects such as hypotension and bradycardia due to peripheral α receptor activation.⁴ Previous studies have shown that the incidence of bradycardia and hypotension ranges from 15% to 27%, and the rates of adverse effects may be higher with infusions longer than 48 hours.³ Hypotension is also more commonly associated with bolus doses of dexmedetomidine.

PICU patients can develop tolerance and physical dependence to sedative and analgesic agents, and withdrawal symptoms can occur if the infusion is abruptly discontinued.⁵ While dexmedetomidine was initially thought to cause little or no withdrawal, a few studies have shown an incidence up to 38%.^{6,7} For monitoring of withdrawal symptoms, the Withdrawal Assessment Tool-1 (WAT-1) is a validated clinical assessment used to determine the extent of withdrawal from opioids and benzodiazepines in critically ill pediatric patients, but it has also been applied to other sedative agents such

as dexmedetomidine.⁸

In the setting of transitioning from a dexmedetomidine infusion for patients at risk of withdrawal, clonidine has been used given its similar mechanism of action as an α_2 -adrenoreceptor agonist.⁶ At our institution there is no formal protocol, and dexmedetomidine infusions are transitioned to clonidine at the discretion of physicians and pharmacists, based on experience and clinical status of the patient. The aim of the present study is to evaluate our use of clonidine for the prevention of withdrawal from dexmedetomidine infusion, and to review current practices at our institution to develop a dose protocol.

Materials and Methods

This was a retrospective review of patients in the PICU at Advocate Children's Hospital, Park Ridge, IL, between January 1, 2015, and August 31, 2017, who received a prolonged dexmedetomidine infusion followed by clonidine weaning. The primary outcome was a description of the clonidine regimen and efficacy of the regimen used to prevent dexmedetomidine withdrawal. This was measured by the need for an increase in sedation during the transition. A need for increase in sedation was defined as an increase in the rate of dexmedetomidine, an increase in the dose or frequency of clonidine, or a rescue dose of clonidine. Secondary outcomes included the incidence of withdrawal, based on WAT-1 scores and symptoms, and the adverse effects of bradycardia and hypotension.

Courses of dexmedetomidine and clonidine were identified by using a report based on drug orders and patient location. Patients were included if they were in the PICU and received continuous dexmedetomidine infusion for at least 72 hours followed by clonidine for at least 48 hours. Patients were excluded if clonidine was a home maintenance medication or they expired during the study period.

Data collected included patient age, sex, weight, dexmedetomidine indication and duration, and dexmedetomidine cumulative, mean, and maximum dose. Dexmedetomidine duration included total infusion days prior to initiation of clonidine, total transition days when receiving both dexmedetomidine infusion and clonidine, and total overall dexmedetomidine infusion days. Clonidine formulation, dose, and frequency were also collected. During the transition from dexmedetomidine to clonidine, the following were collected: clonidine rescue doses, clonidine regimen changes in dose and/or frequency, and dexmedetomidine rate increases.

The WAT-1 scores and symptoms (e.g., fever, vomiting, loose or watery stools, tremor, yawning, sneezing, sweating, agitation) documented in progress notes were collected during both the overlap period of dexmedetomidine and clonidine and the clonidine-only period. WAT-1 scores of 3 or above were considered clinically significant episodes of withdrawal. The pres-

Table 1. Patient Demographics (n = 38)

Parameter	Value
Age, yr, median (IQR)	4.3 (2–11.5)
Male, n (%)	25 (66)
Weight, kg, median (IQR)	19 (11.3–39.4)
Reason for dexmedetomidine, n (%) ^a	
Analgesia	2 (5)
Intubation	29 (76)
Sedation	34 (89)

^a Patients may have had more than 1 indication.

ence of concomitant sedative and opioid infusions and oral opioid and benzodiazepine weaning were also noted. Data were collected during the transition, defined as the period of weaning dexmedetomidine and initiation of clonidine, until one of the following time points was met: 48 hours after the discontinuation of dexmedetomidine and on a stable clonidine dose, defined as zero dose increases, or 72 hours after the discontinuation of dexmedetomidine.

All documented blood pressure and heart rate measurements were collected during the 24-hour period preceding clonidine initiation and the 24-hour period following dexmedetomidine discontinuation to assess for hypotension and bradycardia associated with the transition. An episode of hypotension was defined as a documented systolic blood pressure less than the fifth percentile of the normal range for the patient's age and height. An episode of bradycardia was defined as a documented heart rate less than the second percentile of the normal range for the patient's age and height.⁹ All episodes meeting criteria for hypotension or bradycardia were independently reviewed by the investigators to assess causality due to dexmedetomidine or clonidine versus change in patient clinical condition.

Data were entered and analyzed by using Microsoft Excel 2016 (Impressa Systems, Santa Rosa, CA) and Research Electronic Data Capture (REDCap, version 6.5.15). Descriptive and frequentist statistics were used to analyze the data, and results are reported as median with interquartile range for non-parametric data or mean with standard deviation for parametric data. Least squares linear regression was performed with Microsoft Excel 2016, and a p value of <0.05 was considered statistically significant.

Results

There were a total of 67 courses of dexmedetomidine followed by clonidine for 59 PICU patients between January 1, 2015, and August 31, 2017. Courses were excluded because patients had dexmedetomidine for less than 72 hours (n = 13), received home maintenance clonidine (n = 11), had clonidine for less than 48 hours (n = 3), or expired (n = 1), resulting in 39 courses in 38

Table 2. Concomitant Opioid and Sedative Infusions (36 patients*, 37 dexmedetomidine infusions)

Parameter	Value
Fentanyl	
Number of infusions, n (%)	30 (81)
Concomitant days with dexmedetomidine, mean (range)	6.7 (0.7–19.4)
Midazolam	
Number of infusions, n (%)	28 (76)
Concomitant days with dexmedetomidine, mean (range)	6.3 (0.6–19.5)
Ketamine	
Number of infusions, n (%)	24 (65)
Concomitant days with dexmedetomidine, mean (range)	5.2 (0.04–16)
Hydromorphone	
Number of infusions, n (%)	4 (11)
Concomitant days with dexmedetomidine, mean (range)	4.8 (2–8)

* Two patients did not have concomitant opioid and/or sedative infusions.

patients who met criteria for the study. One patient had 2 courses of dexmedetomidine with weaning to clonidine. Demographics are summarized in Table 1. The median duration of dexmedetomidine infusion was 7.6 days (IQR, 5–11.5), with an average dose of 1 ± 0.5 mcg/kg/hr and median cumulative dose of 141.6 mcg/kg (IQR, 98.4–273). Thirty-six patients received at least 1 concomitant opioid or sedative infusion, and 2 patients received dexmedetomidine alone (Table 2). Four patients received concomitant pentobarbital, and no patients received concomitant morphine.

The transition to clonidine occurred over a median of 0.8 days (IQR, 0–1.4). Clonidine was initiated orally in 95% of cases, most commonly with a dosing frequency of every 8 or 12 hours. The median initial dose of clonidine was 7.8 mcg/kg/day (IQR, 5–12). When stratified by weight, the median initial dose was 8.3 mcg/kg/day for patients weighing less than 50 kg, and 4.1 mcg/kg/day for patients weighing 50 kg or more (Table 3). Higher cumulative dexmedetomidine dose was significantly correlated with higher initial clonidine dose when the duration of dexmedetomidine exposure was at least 7 days ($p = 0.02$). Regression analysis demonstrated that in these patients, every 100 mcg/kg of cumulative dexmedetomidine was associated with a 1.8-mcg/kg/day initial clonidine dose (Figure 1). Higher mean dexmedetomidine dose (mcg/kg/hr) in the 24 hours prior to clonidine initiation also correlated significantly with higher initial clonidine dose ($p = 0.04$). Regression analysis showed that every 1 mcg/kg/hr mean dexmedetomidine dose in the 24 hours prior to clonidine initiation was associated with an initial clonidine dose of 3.5 mcg/kg/day (Figure 2). Regression analyses are limited by the data and do not extend infinitely in either direction.

A total of 7 patients (18%) with elevated WAT-1 scores

(≥ 3) required an increase in sedation during the transition period or after dexmedetomidine was discontinued (Figure 3). Three patients required an increase in sedation in both periods. For patients who had an increase in the dexmedetomidine infusion, an increase of 0.2 to 0.25 mcg/kg/hr was observed, or the infusion was discontinued and restarted shortly after. For patients who had a change in their clonidine regimen, the dose was increased by 50% to 100%. The number of rescue doses of clonidine ranged from 1 to 13. WAT-1 scores were missing for 13 patients during the transition period and for 7 patients during the clonidine-only period. While receiving clonidine, there were 16 patients receiving concomitant weaning with methadone and lorazepam, 11 patients receiving methadone alone, and 5 patients receiving lorazepam alone. Common documented withdrawal symptoms were agitation and

Table 3. Initial Clonidine Regimen

Parameter	Value
mcg/kg/DOSE, median (IQR)	
<50 kg	4.2 (2.4–5.8)
≥ 50 kg	1.5 (1.1–1.7)
mcg/kg/DAY, median (IQR)	
<50 kg	8.3 (6.2–14.9)
≥ 50 kg	4.1 (2.3–5.2)
Route of administration, n (%)	
Oral	37 (95)
Transdermal	2 (5)
Dosing intervals, n (%)	
Daily	2 (5)
Every 6 hr	1 (3)
Every 8 hr	23 (59)
Every 12 hr	11 (28)
Every week	2 (5)

Figure 1. Longer duration of dexmedetomidine infusions correlated with higher initial clonidine doses.

$R^2 = 0.27$.

diarrhea (Table 4).

Hypotensive events occurred in 8 of 39 (21%) infusions during the 24 hours preceding clonidine initiation; 2 (25%) were possibly related to dexmedetomidine. Hypotensive events occurred in 9 of 39 (23%) infusions during the 24 hours after dexmedetomidine was discontinued; 2 (22%) were possibly related to clonidine. The 4 events occurred in a total of 3 patients, and none required an intervention. Bradycardic events occurred in 10 of 39 (26%) infusions during the 24 hours preceding clonidine initiation; 1 (11%) was possibly related to dexmedetomidine. Bradycardic events occurred in 8 of 39 (21%) infusions during the 24 hours after dexmedetomidine

was discontinued; 1 (11%) was possibly related to clonidine. The 2 events occurred in the same patient, and dexmedetomidine was decreased. Based on the Naranjo adverse drug event scoring, events were possibly related to dexmedetomidine or clonidine.

Discussion

Dexmedetomidine infusions in pediatric patients serve as a means of titratable sedation without adversely affecting respiratory drive, potentially allowing for decreased opioid and benzodiazepine requirements. The transition from prolonged dexmedetomidine to clonidine

Figure 2. Higher mean dexmedetomidine doses during the 24 hours prior to transitioning clonidine correlated with higher initial clonidine doses.

$R^2 = 0.11$.

Figure 3. (A) During the transition, when dexmedetomidine and clonidine overlap. (B) During the clonidine-only period.**A** **B**

WAT-1, Withdrawal Assessment Tool-1

dine to prevent withdrawal is less defined, and practice is variable. With this retrospective analysis, we aimed to describe the use of clonidine as means of weaning from dexmedetomidine. We defined prolonged infusion of dexmedetomidine as 72 hours or longer to best capture patients who were likely transitioned to clonidine. The minimum duration of 48 hours of clonidine was to ensure patients achieved adequate exposure during the transition period. The initial clonidine dose was correlated with the cumulative dexmedetomidine dose and the average dexmedetomidine dose 24 hours prior to beginning clonidine. We also found that increases in sedation due to withdrawal (WAT-1 scores ≥ 3) were necessary in 7 (18%) patients. Hypotensive and bradycardic events possibly due to dexmedetomidine and clonidine were infrequent and required intervention in only 1 patient. While our dosing relationships to determine the initial clonidine dose are estimates with limitations, overall the transition to clonidine was safe and efficacious with minimal adverse cardiovascular effects in our patients.

The analysis by Lardieri et al⁶ in pediatric patients receiving dexmedetomidine for 5 days or longer showed a trend toward fewer elevated WAT-1 scores when patients were weaned to clonidine compared to those who were not weaned. The mean clonidine initiation dose was 9 mcg/kg/day (range, 2.9–18.2), similar to our finding of 9.3 mcg/kg/day (range, 1.3–18.8). Although their population was younger and the patients received clonidine transdermally, the consistency of the results suggests an appropriate clonidine dose range for dexmedetomidine withdrawal. We had further stratified the initial clonidine dose by weight (median of 8.3 mcg/kg/day for patients <50 kg, and 4.1 mcg/kg/day for patients ≥ 50 kg) to determine if/when dosing tended to mimic adult doses. The determination of 50 kg was an estimate, but results did not differ greatly if 40 kg was used instead. Most of our patients received clonidine orally (tablets or 100 mcg/mL compounded suspension) for ease in titrating and tapering regimens.

Converting shorter-acting continuous infusions to longer-acting intermittent agents has been used as a

Table 4. Withdrawal Symptoms

Symptom	n (%)
Agitation	30 (77)
Diarrhea	26 (67)
Sweating	17 (44)
Yawning/sneezing	17 (44)
Tremor	16 (41)
Fever	13 (33)
Vomiting	13 (33)

strategy to prevent withdrawal from opioids and benzodiazepines. Our institution has recommended sedation weaning guidelines for opioids and benzodiazepines but no formalized guideline for clonidine conversion. The advantages in transitioning dexmedetomidine to clonidine include removal of intravenous lines, decreasing PICU level care, and transferring to the general floor for further management. Our analysis showed that higher initial clonidine doses were required when patients were exposed to dexmedetomidine for 7 days or longer, resulting in higher cumulative doses. Every 100 mcg/kg of cumulative dexmedetomidine was associated with a 1.8-mcg/kg/day initial clonidine dose. The cumulative dose is a marker for overall dexmedetomidine exposure. In addition, patients receiving higher dexmedetomidine doses prior to the transition also required higher initial clonidine doses. Every 1 mcg/kg/hr mean dexmedetomidine dose in the 24 hours preceding clonidine initiation was associated with a 3.5-mcg/kg/day initial clonidine dose. These relationships have inherent limitations that need to be considered. The linear regression equations cannot reasonably be extended indefinitely in either direction, and may not be appropriate if used in combination. In our patients exposed to dexmedetomidine for less than 7 days, these correlations were not apparent; there was no linear relationship between cumulative dexmedetomidine dose and initial clonidine dose. Our regression analyses also did not account for the effect of concomitant opioid and benzodiazepine sedatives or concomitant weaning. The initial clonidine regimen should be individualized to the patient, using these correlations as a guide or frame of reference.

To observe the effectiveness of the clonidine regimen, we looked at increases in sedation as a marker for adequate weaning from dexmedetomidine. Seven patients required increases in dexmedetomidine dose, clonidine regimen, and/or received a clonidine rescue dose during the transition. Given the retrospective nature of the study, an increase in sedation was considered to be a response to withdrawal (elevated WAT-1 score ≥ 3) or a clinical change in the patient documented in the progress notes. Seven patients required an increase in the transition period, and 3 patients required

an increase during the clonidine-only period (3 patients accounted for increases in both periods). Some patients with elevated WAT-1 scores did not require any intervention. Although the time to onset of withdrawal and need for increased sedation was assessed, there was a wide variability from less than 24 hours to nearly 72 hours after dexmedetomidine was discontinued. Since only 7 patients required an intervention, and the dexmedetomidine weaning was not standardized, it is challenging to make a meaningful conclusion regarding which agent was the culprit.

Furthermore, the WAT-1 is a validated scoring system for withdrawal from opioids and benzodiazepines. Its use for dexmedetomidine withdrawal is based on extrapolation.⁸ It is validated for use at least once per 12-hour shift. In some of our patient cases, WAT-1 scores were being documented every 2 to 4 hours with vital signs, possibly overstating patient symptoms. The WAT-1 scores were added to the electronic health record at our institution in 2015 to facilitate documentation. Despite this, not all patients had WAT-1 scores recorded in the charts, resulting in substantial amount of missing data (34%). In addition, our predefined increases in sedation focus only on the changes to dexmedetomidine and clonidine regimens. Many patients were on concomitant opioid and benzodiazepine infusions and weaning that may have confounded the ability to adequately attribute withdrawal symptoms specifically to dexmedetomidine. At our institution, dexmedetomidine is generally not weaned until opioid and benzodiazepine infusions are discontinued, and patients are receiving stable doses of oral methadone or morphine and lorazepam.

Dexmedetomidine and clonidine have known effects on blood pressure and heart rate due to their activity on peripheral α receptors in the vascular smooth muscle. The incidence of hypotension and bradycardia in our study was minimal, with only 1 patient requiring a decrease in the dexmedetomidine dose as a result. Since dexmedetomidine boluses are not used at our institution, that was not the cause, but assessing hypotensive and bradycardic episodes retrospectively proves challenging. By using the quantitative parameters of the fifth percentile for systolic blood pressure and the second percentile for heart rate of the normal ranges for age and height, we attempted to measure these adverse cardiovascular episodes objectively. Two 24-hour periods, prior to clonidine initiation and after dexmedetomidine discontinuation, were chosen to assess blood pressure and heart rate before and after the transition in an effort to attribute any changes to either dexmedetomidine or clonidine and minimize confounding variables during the transition itself. Several variables can still confound the mechanism of the patient's hypotension or bradycardia. Including all numerically defined episodes as clinically significant may be an overestimate. Some patients have low

blood pressure or heart rate at baseline, or their vital signs may fluctuate with their circadian rhythms. While their blood pressure or heart rate is numerically low, their clinical status could be stable. Patients may also be hypotensive or bradycardic as a result of other nursing interventions (e.g., suctioning, repositioning) or underlying pathology. These scenarios are complicated to assess retrospectively. Thus, to minimize the confounding variables, the investigators independently reviewed each numerically defined episode of hypotension or bradycardia, and excluded the ones likely attributable to another cause, leaving episodes possibly due to dexmedetomidine or clonidine. Although the Naranjo scoring system was used to better estimate the likelihood, the algorithm also has inherent limitations. Inconsistent documentation, whether too frequent or lacking, is also a limitation here. Frequency of vital signs is variable in the PICU, depending on the stability of the patient, which resulted in some patients having more data than others. Despite these limitations, our study supports existing literature that dexmedetomidine is generally well tolerated.

Conclusions

Our analysis demonstrated that pediatric patients at our institution, receiving an average of 1 mcg/kg/h of dexmedetomidine, could be safely transitioned to clonidine at doses of approximately 8 mcg/kg/day to prevent withdrawal. Although patients may respond differently and the transition to clonidine needs to be individualized, the results of our analysis may be beneficial, as the current literature on the subject is sparse. In addition, these results can be used to create a standardized protocol at our institution to help guide the transition from dexmedetomidine infusion to clonidine. While our analysis determines considerations and dosing ranges for the initial clonidine regimen, further study is needed to better elucidate the effectiveness while controlling for other causes of withdrawal, as well as the duration of clonidine for this indication. Prospective studies with larger patient samples across multiple institutions would be of benefit.

ARTICLE INFORMATION

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Michelle Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee at Advocate Health Care did not require HIPAA Authorization, Assent, and Parental Permission under Expedited criterion.

Acknowledgments This project was presented at the Advocate Children's Hospital Pediatric Research and Quality Improvement Symposium in Oak Lawn, IL, on May 16, 2018. The authors would like to thank Yi Li, MS, for her statistical expertise on this project.

Accepted September 5, 2019

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