Clinical Investigation

Effects of Clonidine on Withdrawal From Long-term Dexmedetomidine in the Pediatric Patient

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OBJECTIVE: To compare withdrawal symptoms among pediatric intensive care patients receiving clonidine to those not receiving clonidine while being weaned from long-term dexmedetomidine.

METHODS: This retrospective analysis evaluated Withdrawal Assessment Tool-1 (WAT-1) scores and hemodynamic parameters in pediatric patients on dexmedetomidine for 5 days or longer between January 1, 2009, and December 31, 2012. The primary objective was to compare withdrawal symptoms based on the number of elevated WAT-1 scores among patients on clonidine to those not on clonidine, while being weaned from long-term dexmedetomidine. The secondary objective was to describe withdrawal symptoms associated with long-term dexmedetomidine use.

RESULTS: Nineteen patients (median age, 1.5 years; interquartile range [IQR], 0.67-3.3) received 20 treatment courses of dexmedetomidine for at least 5 days. Clonidine was received by patients during 12 of the treatment courses. The patients in the clonidine group had an average of 0.8 (range, 0-6) elevated WAT-1 scores 24 hours post wean compared to an average of 3.2 (0-8) elevated WAT-1 scores in the no clonidine group ($p = 0.49$). There were no significant differences between prewean and postwean systolic or diastolic blood pressures among the 2 groups. The average heart rate during the postwean period was 112 beats per minute (bpm) (range, 88.5-151.5) in the clonidine group compared to 138.4 bpm (range, 117.8-168.3) in the no clonidine group ($p = 0.003$). In the clonidine group, the mean change in heart rate postwean compared to prewean was an increase of 3.6 bpm (range, −39.6 to 47.5), compared to a mean increase of 29.9 bpm (range, 5.5-74.7) in the no clonidine group ($p = 0.042$).

CONCLUSIONS: There was no difference in WAT-1 scores between groups, with the clonidine group displaying a trend towards fewer elevated WAT-1 scores during the 24 hours post dexmedetomidine wean. Patients who received clonidine had significantly lower heart rates than the no clonidine group.

INDEX TERMS: clonidine, dexmedetomidine, sedation, tachycardia, withdrawal

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INTRODUCTION

Dexmedetomidine and clonidine are centrally acting α_2-adrenergic agonists that exhibit sedative, anxiolytic, and analgesic properties. Both contain an imidazole ring, and display a high specificity for the α_2 receptor over the α_1 receptor; however, dexmedetomidine exerts a specificity of 1600:1 for the α_2:α_1 receptor, whereas the specificity of clonidine is 200:1. Dexmedetomidine's shorter half-life of 2 to 3 hours, compared to clonidine's half-life of 8 to 12 hours in children allows for titration via continuous infusion. The labeled dosage range for intensive care unit sedation for adult patients is 0.2 to 0.7 mcg/kg/hr; however, maintenance doses as large as 1 mcg/kg/hr have been described in pediatric studies.[1,2] Infusion rates as large as 2.5 mcg/kg/hr have been used, but it is thought that doses larger than 1.5 mcg/kg/hr may not contribute to additional efficacy.[3] Given its novel mechanism of action, beneficial physiologic effects and favorable adverse effect profile, dexmedetomidine is being used increasingly in the pediatric patient

population, particularly in pediatric critical care and pediatric anesthesia. [4,5] Studies detailing the use of dexmedetomidine in the pediatric population demonstrate that it provides adequate sedation and anxiolysis while minimally affecting respiratory response. [6,7] Tobias and Berkenbosch[8] demonstrated that the use of dexmedetomidine compared to midazolam in mechanically ventilated children and infants reduced the need for morphine boluses to provide more effective sedation. In addition, dexmedetomidine has the potential to reduce opioid and benzodiazepine use and reduce the total duration of mechanical ventilation.[3,6,8,9]

Tolerance and physical dependency are known to occur with analgesic and sedative agents in the pediatric intensive care setting.[10,11] Abrupt discontinuation of these agents after prolonged infusions leads to withdrawal symptoms. Initially, there was speculation that dexmedetomidine would be associated with limited or no development of tolerance or withdrawal.[12,13] However, due to its similar structure and mechanism of action to clonidine and reports of withdrawal from clonidine, it is likely that long-term use of dexmedetomidine would also result in withdrawal symptoms if not weaned appropriately.[14,15] Dexmedetomidine's withdrawal effects after long-term use in pediatric patients have not been well described. Case reports and retrospective case series in pediatric patients have described withdrawal symptoms such as tachycardia, hypertension, and agitation following the use of dexmedetomidine for 3 or more days; however, none of these reports used an objective measure of withdrawal to quantify the nature of the symptoms.[16–20]

Due to clonidine's similar mechanism of action to dexmedetomidine and its effectiveness in treating neonatal abstinence syndrome, an evolving practice in the pediatric intensive care unit (PICU) at the University of Maryland Children's Hospital (UMCH) involves using clonidine to reduce withdrawal from long-term dexmedetomidine.[21,22] Additionally, due to the objectivity and validity of the Withdrawal Assessment Tool-1 (WAT-1) in evaluating withdrawal from opioids and benzodiazepines in pediatric patients, the WAT-1 is routinely used to evaluate withdrawal in our PICU.[23,24] With the paucity of literature regarding long-term dexmedetomidine and withdrawal, we performed a retrospective chart review to analyze our institution's use of clonidine with dexmedetomidine and how this adjunctive therapy affects withdrawal symptoms among pediatric patients. We used the WAT-1 score to objectively measure withdrawal symptoms experienced by pediatric patients.

The purpose of this study was to evaluate withdrawal in pediatric patients who were weaned from long-term dexmedetomidine. The primary objective was to compare withdrawal symptoms based on the number of elevated WAT-1 scores among patients on clonidine to those not on clonidine, while being weaned from long-term dexmedetomidine. A secondary objective was to describe the withdrawal symptoms experienced after long-term dexmedetomidine use. We hypothesized that patients receiving clonidine while being weaned from long-term dexmedetomidine experience less withdrawal compared to those who did not receive clonidine.

MATERIALS AND METHODS

This was a retrospective, single-center study evaluating withdrawal in pediatric patients who were being weaned from long-term dexmedetomidine. Institutional review board approval was obtained and consent was waived. All patients admitted to the UMCH PICU and intubated for acute respiratory failure between January 1, 2009, and December 31, 2012, were reviewed for inclusion. The UMCH is a children's hospital within a tertiary care academic medical center, and the PICU admits approximately 1200 patients annually.

All children who were at least 2 weeks of age, ≥ 42 weeks' gestational age, ≤ 18 years of age, supported on mechanical ventilation for acute pulmonary disease, and received continuous infusion dexmedetomidine for at least 5 days were eligible for inclusion. Patients with cyanotic heart disease, primary pulmonary hypertension, neuromuscular respiratory failure, or who were ventilator-dependent on PICU admission were excluded. Patients who had their pain managed on a patient-controlled analgesia (PCA) pump or epidural or who were transferred from an outside hospital where sedatives were already administered for at least 24 hours were also excluded. At our institution, dexmedetomidine is initiated after failure of conventional sedation regimens including continuous infusion opioids and ben-

zodiazepines, and currently there is no standard protocol for discontinuation of dexmedetomidine. The typical rate of weaning for dexmedetomidine is to decrease the dose by 0.2 to 0.5 mcg/kg/hr with changes made every 12 hours and a goal of reaching 0.2 to 0.5 mcg/kg/hr prior to discontinuation; however, the actual decrease in dose is at the discretion of the attending physician. The attending physician made the decision to initiate clonidine and which formulation to use. If a clonidine patch is used, the patch is applied at least 2 days prior to initiating the dexmedetomidine wean. Patients were divided into 2 groups: those who received transdermal or enteral clonidine while being weaned from dexmedetomidine, and those who did not.

The primary objective was to compare withdrawal symptoms based on the number of elevated WAT-1 scores among patients on clonidine to those not on clonidine, while being weaned from long-term dexmedetomidine. Long-term dexmedetomidine use was defined as ≥ 5 days. Withdrawal Assessment Tool-1 scores were recorded by the bedside nurse every 4 to 6 hours while sedation medications are being weaned, as per our PICU standard practice. Withdrawal Assessment Tool-1 scoring includes an assessment of loose or watery stools; vomiting, retching, or gagging; temperature > 37.8°C; a 2-minute prestimulus observation of state, tremor, sweating, uncoordinated movement, yawning, or sneezing; a 1-minute stimulus observation of startle to touch and muscle tone; and a poststimulus recovery of time to gain a calm state. The score ranges from 0 to 12, with a score of 3 or greater being indicative of withdrawal. The primary outcome of withdrawal was assessed by the number of elevated WAT-1 scores. Elevated WAT-1 scores were defined as those ≥ 3 during the 24 hours postwean. Since the terminal half-life of dexmedetomidine is 2 hours, data were collected for 24 hours postwean, which allows for 14 hours after the drug has theoretically been cleared from the body. Secondary outcomes included the incidence of rebound hypertension and rebound tachycardia during the 24 hours postwean. Rebound hypertension and rebound tachycardia were defined as an increase by 20% or more compared to the prewean time period. The mean blood pressure and heart rate during the 24 hours prewean and postwean was utilized in the comparison.

The following data were collected: patient demographics, duration of dexmedetomidine, cumulative dexmedetomidine dose, mean dexmedetomidine dose, maximum dexmedetomidine dose, clonidine formulation used, clonidine dose at initiation, total dexmedetomidine infusion days when clonidine initiated, WAT-1 scores during the 24 hours post wean, and hemodynamics (blood pressure and heart rate during the 24 hours pre- and postwean). Prewean was defined as the 24 hours before the dexmedetomidine wean began, and postwean was defined as the 24 hours after the dexmedetomidine infusion was stopped. Descriptive statistics were used to characterize the population. Wilcoxon signed rank test was used to compare the primary and secondary outcomes and other variables. A p value of < 0.05 was considered significant.

RESULTS

Nineteen patients received dexmedetomidine for at least 5 days and met inclusion criteria. One patient received 2 separate courses of dexmedetomidine separated by 15 days, thus there were 20 dexmedetomidine treatment courses. Patients received clonidine during 12 of the treatment courses and did not receive clonidine during 8 of the treatment courses.

The demographic data between the 2 groups was not significantly different. Six of 12 (50.0%) patients in the clonidine group were male, and 5 of 8 (62.5%) patients in the no clonidine group were male (p = 0.67) (Table 1). Median age was 1.5 years (interquartile range [IQR], 0.67-3.3) in the clonidine group compared to 1.0 year (IQR, 0.85-1.3) in the no clonidine group (p = 0.624). The median ICU length of stay in the clonidine group was 16.6 days (IQR, 13.2-26.9) compared to 12.9 (IQR, 9.8-20.3) in the no clonidine group (p = 0.181). Hospital length of stay and ventilator days were not significantly different between groups (Table 2).

The duration of dexmedetomidine significantly differed between the clonidine and no clonidine groups (Table 3). The median duration of dexmedetomidine in the clonidine group was 241.8 hours (IQR, 185-406.3) or 10 days, and the median duration in the no clonidine group was 134.5 hours (IQR, 117-144) or 5.5 days (p = 0.003). Because the overall duration of dexmedetomidine differed, the cumulative dose also

Table 1. Patient Demographics

Treatment Courses (n = 20)	Clonidine (n = 12)	No Clonidine (n = 8)	p-Value
Male, n (%)	6 (50%)	5 (62.5%)	0.670
Age (yr)*	1.5 (0.67-3.3)	1.0 (0.85-1.3)	0.624
Weight (kg)*	12.3 (8.0-19.0)	9.8 (8.5-12.3)	0.521

** Median (interquartile range)*

was significantly different between groups. The mean dose throughout the full course of therapy prior to weaning in both groups was similar at 1 mcg/kg/hr (p = 0.910).

All 12 patients who received clonidine received it as the transdermal formulation. Clonidine patches were placed on average 5.6 days before dexmedetomidine discontinuation. Eleven of 12 patients were initiated on the 100 mcg/24 hr patch, and 1 patient was initiated on 50 mcg/24 hr using half of a 100-mcg patch, by covering half of the patch with a Tegaderm.[25] The mean clonidine dose at initiation was 9 mcg/kg/day (range, 2.9-18.2). Two of 12 patients had increases in their clonidine doses throughout treatment; one increased to a 200-mcg/24 hr patch (10.5 mcg/kg/day), and the other increased to a 300-mcg/24 hr patch (15.4 mcg/kg/day). These 2 patients were on extended duration and larger doses of dexmedetomidine: 15 days with a maximum dose of 1.8 mcg/kg/hr and 45 days with a maximum dose of 1.5 mcg/kg/hr, respectively. Clonidine was initiated on day 7 of dexmedetomidine infusion on average (range, 5-9).

Withdrawal Assessment Tool-1 scores were documented in 11 of 12 patients in the clonidine group and 6 of 8 patients in the no clonidine group. Patients with no WAT-1 scores were not included in the primary outcome analysis. For the primary outcome of withdrawal, the patients in the clonidine group had a mean of 0.8 (range, 0-6) elevated WAT-1 scores compared to a mean of 3.2 (0-8) elevated WAT-1 scores in the no clonidine group (p = 0.49) during the 24 hours postwean. In the clonidine group, 4 of 11 (36.4%) patients had an elevated WAT-1 score compared to 4 of 6 (66.7%) patients in the no clonidine group. In the no clonidine group, the 4 patients had a total of 14 elevated WAT-1 scores. The elevated WAT-1 scores in the no clonidine group were most commonly being scored for tremor (15), uncoordinated repetitive movements (15), time to gain calm state (13), state behavioral scale (SBS) greater than +1 (12), startling to touch (9), and increased muscle tone. On the day of dexmedetomidine wean, 5 of 12 (41.7%) patients in the clonidine group were also weaned from an opioid, and in the no clonidine group, 3 of 8 (37.5%) patients were weaned from an opioid (p = 1.00). Four of 12 (33.3%) patients in the clonidine group were also weaned from a benzodiazepine on the day of dexmedetomidine wean, and in the no clonidine group, 2 of 8 (25%) patients were weaned from a benzodiazepine (p = 1.0).

There were no significant differences in terms of prewean and postwean mean systolic or diastolic blood pressures between the 2 groups (Table 4). Two of 12 (16.7%) patients in the clonidine group experienced rebound systolic hypertension during the 24 hours post wean compared to zero patients in the no clonidine group. Four of 12 patients (33.3%) in the clonidine group experienced rebound diastolic hypertension during the 24 hours post wean compared to 1 of 12 (12.5%) patients in the no clonidine group. These were not significantly different.

Patients who received clonidine did have significantly lower mean heart rates during the 24-hour postwean period compared to the no clonidine group (Table 4 and Figure). The mean heart rate during the postwean period was 112 beats per minute (bpm) (range, 88.5-151.5) in the clonidine group compared to 138.4 bpm (range, 117.8-168.3) in the no clonidine group (p = 0.003). The mean change in heart rate from the postwean period compared to the prewean period was an increase of 3.6 bpm (range, −39.6 to 47.5) in the clonidine group, and an increase of 29.9 bpm (range, 5.5-74.7) in the no clonidine group (p = 0.042). Rebound tachycardia was noted in both groups.

DISCUSSION

This study was designed to determine whether pediatric patients who received clonidine expe-

Table 2. Patient Characteristics and Outcomes

Treatment Courses (n = 20)	Clonidine (n = 12)	No Clonidine (n = 8)	p-Value
Admission Diagnosis, n (%)			
Respiratory failure/distress	5 (41.7%)	4 (50%)	1.000
Pneumonia	2 (25%)	3 (37.5%)	0.642
RSV	2 (16.7%)	0 (0%)	0.495
Asthma	1 (8.3%)	0 (0%)	1.000
Other	1 (8.3%)	1 (12.5%)	1.000
LOS (days), median (IQR)	29.1 (22.0-35.9)	19.9 (16.0-28.7)	0.270
ICU LOS (days), median (IQR)	16.6 (13.2-26.9)	12.9 (9.8-20.3)	0.181
Ventilator days, median (IQR)	12.3 (10.5-20.3)	7.5 (6.5-14.4)	0.115

ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; RSV, respiratory syncytial virus

rienced less withdrawal symptoms when being weaned from long-term dexmedetomidine compared to patients who did not receive clonidine. We found that patients treated with clonidine trended towards having fewer elevated WAT-1 scores compared to the no clonidine group and experienced less tachycardia while weaning from dexmedetomidine. Although there was no statistical difference in WAT-1 scores between empiric clonidine and no clonidine treatment to facilitate dexmedetomidine weaning, the trend towards fewer elevated scores in the first 24 hours may be clinically relevant to this patient population.

The patients who received clonidine in our population were on dexmedetomidine for a longer duration of time, approximately 10 days compared to approximately 5 days in the no clonidine group. This difference was expected as patients are more likely to be initiated on clonidine by the attending physician if they are receiving dexmedetomidine for an extended period of time. These patients who had longer durations of dexmedetomidine and thus larger cumulative doses would theoretically be at an increased risk of withdrawal. The fact that we saw a trend towards fewer elevated WAT-1 scores in this group of patients suggests the adjunctive use of clonidine may have minimized their withdrawal symptoms. A study with a larger patient population is needed to confirm this.

Previous studies in pediatric patients have shown that methadone has been effective in preventing withdrawal associated with long-term narcotics used for sedation.[26–28] The principle of using a longer-acting agent with a similar mechanism to the shorter-acting continuous infusion to help reduce withdrawal symptoms can be applied to our use of clonidine to minimize withdrawal from dexmedetomidine. Clonidine ameliorates autonomic overactivity such as tachycardia, hypertension, diaphoresis, restlessness, and diarrhea in neonates experiencing withdrawal.[21,29,30] Clonidine has also been used in the PICU setting as an adjunctive agent to treat withdrawal from opioids, benzodiazepines, and

Table 3. Dexmedetomidine Use

Dexmedetomidine Treatment Courses (n = 20)	Clonidine (n = 12)	No Clonidine (n = 8)	p-Value
Duration of dexmedetomidine (hr), median (IQR)	241.8 (185-406.3)	134 (117-144)	**0.003**
Cumulative dose (mcg/kg), median (IQR)	232.7 (158.3-336.1)	126.1 (102.1-157.5)	**0.031**
Mean dose* (mcg/kg/hr), range	1.0 (0.53-1.81)	1.0 (0.42-1.73)	0.910
Maximum dose (mcg/kg/hr), median (IQR)	1.5 (1.0-1.85)	1.25 (1.1-1.5)	0.406
Absolute maximum dose used (mcg/kg/hr)	2.2	2.0	0.521

IQR, interquartile range
** Mean dose throughout full course of therapy prior to wean*

Table 4. Blood Pressure and Heart Rate

Dexmedetomidine Treatment Courses (n = 20)	Clonidine (n = 12)	No Clonidine (n = 8)	p-Value
Systolic Blood Pressure (mmHg)			
Prewean, mean (range)	100.1 (86.5-116.6)	99.5 (83.6-130.0)	0.624
Postwean, mean (range)	102.6 (73.2-123.8)	104.7 (91.8-118.3)	0.851
Rebound systolic hypertension, n (%)	2 (16.7%)	0 (0%)	0.495
Diastolic Blood Pressure (mmHg)			
Prewean, mean (range)	52.7 (41.2-62.5)	53.2 (46.4-65.0)	0.910
Postwean, mean (range)	56.3 (37.0-67.3)	58.7 (50.5-70.7)	0.678
Rebound diastolic hypertension, n (%)	4 (33.3%)	1 (12.5%)	0.603
Heart Rate (bpm)			
Prewean, mean (range)	108.4 (85.8-149.3)	108.6 (93.7-131.8)	0.851
Postwean, mean (range)	112.0 (88.5-151.5)	138.4 (117-168.3)	**0.003**
Change from postwean compared to prewean, mean (range)	3.6 (−39.6 to 47.5)	29.9 (5.5-74.7)	**0.042**
Rebound tachycardia, n (%)	3 (25%)	4 (50.0%)	0.356

bpm, beats per minute

chloral hydrate.[22,25,26,31–33] It has been suggested that pediatric patients who receive dexmedetomidine infusions for longer than 4 to 5 days might benefit from a switch to an equivalent dose of oral or transdermal clonidine, although this equivalent dose has not been established.[34] Based on our population, a recommendation of 8 to 10 mcg/kg/day of clonidine could be considered for patients on dexmedetomidine for 5 days or longer at a mean dose of 1 mcg/kg/hr. A clonidine patch may be preferred due to its pharmacokinetic properties of a slow and even release of drug. The elimination half-life for the transdermal formulation is approximately 20 hours, which reduces the risk for the abrupt withdrawal that is possible with the oral formulation. However, the onset of action can be prolonged at 48 hours, necessitating some form of bridging with oral clonidine or dexmedetomidine during this period of time. In our patients, dexmedetomidine was not weaned until 48 hours after application of the clonidine patch.

Characterization of withdrawal from dexmedetomidine has been reported in pediatric case reports and retrospective studies.[16–20] Burbano et al[20] described tachycardia, agitation, and transient hypertension in their retrospective case series of 62 pediatric cardiac patients after discontinuation of prolonged infusions of dexmedetomidine. Although they defined long-term as 3 days compared to our definition of 5 days, our dosing range and mean duration of treatment was similar. Beijian et al[16] found no significant changes in hemodynamics after abruptly terminating dexmedetomidine infusions in their retrospective chart review of 54 pediatric cardiac patients. However, their mean dose of 0.4 to 0.8 mcg/kg/hr was much lower than both our mean dose of 1.0 mcg/kg/hr and Burbano and colleagues,[20] range of dosing of 0.7 to 2.1 mcg/kg/hr. The mean duration of dexmedetomidine in Beijian and colleagues'[16] patient population was 37.3 hours, shorter than ours and Burbano's as well. In our patients who did not receive clonidine, the most common reasons for elevated WAT-1 scores were SBS greater than +1, uncoordinated repetitive movements, tremor, and time to gain calm state.

Our study suggests clonidine may be useful to prevent elevated WAT-1 scores in the first 24 hours after discontinuation of dexmedetomidine in the homogenous respiratory failure population admitted to a PICU and can reduce tachycardia during this time period. Two cases of acute dexmedetomidine withdrawal syndrome were successfully treated with oral clonidine in adult medical ICU patients.[35] Our study is the first to examine clonidine use for dexmedetomidine withdrawal in the pediatric population. Based on our results, transdermal clonidine initiated on day 5 of dexmedetomidine infusion may reduce withdrawal symptoms including tachycardia; however, it is possible that initiating clonidine earlier during dexmedetomidine infusion may

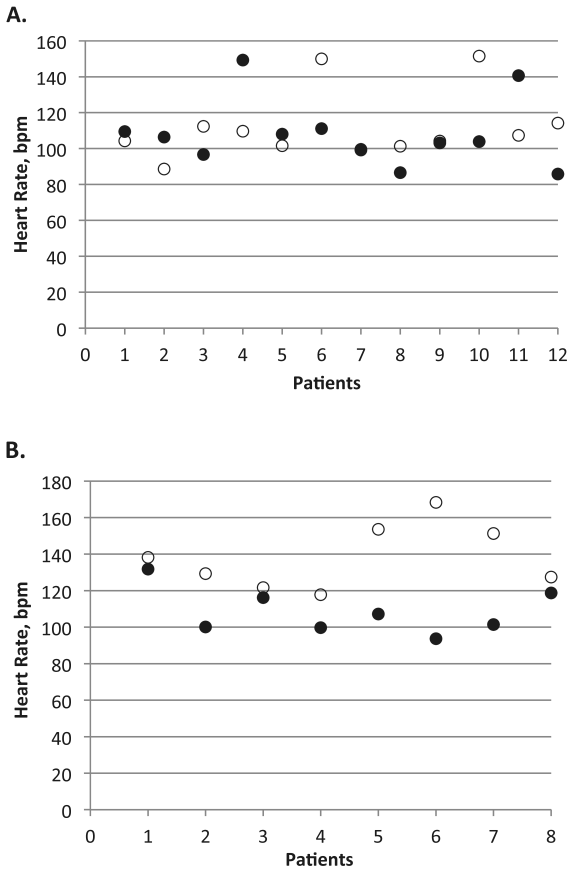

Figure. Mean heart rate in clonidine (A) and no clonidine (B) groups during 24 hr post dexmedetomidine wean. ● = prewean heart rate; ○ = postwean heart rate.

have additional benefit. This warrants further evaluation. The mean dose of clonidine utilized in our patient population of 9 mcg/kg/day is similar to what has been reported for neonatal abstinence syndrome.[36] All of our patients received the transdermal formulation of clonidine, which prevents issues with the oral formulation. Some of these issues include compounding an oral suspension and dosing more frequently at 3 to 4 times per day. Since the transdermal formulation should not be cut, smaller doses can be achieved by covering half of the patch with a tegaderm. However, this is not an exact method. Clonidine patches may need to be changed every 3 to 5 days in children. Another benefit of the transdermal formulation is the potential for less adverse effects due to the lower peak to trough ratio.

There are limitations to the current study. The patient population is small, likely due to the stringent inclusion and exclusion criteria utilized to identify a more homogeneous patient population of those being mechanically ventilated for acute pulmonary disease. Patients who received clonidine trended towards a longer ICU and hospital length of stay compared to patients who did not receive clonidine. However, the data collected are important to disseminate as there is very limited information available regarding the use of clonidine for dexmedetomidine withdrawal. There was a baseline difference between the 2 groups in regards to the duration of dexmedetomidine use. However, since we actually saw a numerically lower number of elevated WAT-1 scores in the patients in the clonidine group who were on longer durations of dexmedetomidine, perhaps this baseline difference is not a limitation. Withdrawal Assessment Tool-1 scores were not documented for all patients, and were missing in 1 patient in the clonidine group and in 2 patients in the no clonidine group. The WAT-1 tool was developed for assessing opioid and benzodiazepine withdrawal symptoms, and we extrapolated its use to dexmedetomidine withdrawal; however, heart rate and blood pressure, which is not documented on this scoring tool, was examined separately. Opioid and benzodiazepines were also weaned on the same day as dexmedetomidine in some patients, which could have been contributing to their withdrawal symptoms. However, there were no differences between groups in terms of the number of patients being weaned from other sedation medications on the same day as the dexmedetomidine wean.

CONCLUSION

In this retrospective analysis, patients who received clonidine while being weaned from long-term dexmedetomidine trended towards having fewer withdrawal symptoms by an objective measure of withdrawal compared to the patients who did not receive clonidine. Patients who received clonidine had significantly lower heart rates while being weaned from long-term dexmedetomidine. Future investigations would ideally include a larger sample size by increasing the study duration or by collaborating with multiple PICUs. Further pediatric studies are warranted to clearly define dosing, initiation time, and duration for clonidine use in managing withdrawal from dexmedetomidine in critically ill children.

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Abbreviations bpm, beats per minute; IQR, interquartile range; PCA, patient-controlled analgesia; PICU, pediatric intensive care unit; SBS, state behavioral scale; UMCH, University of Maryland Children's Hospital; WAT-1, Withdrawal Assessment Tool-1

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