The Impact of a Clonidine Transition Protocol on Dexmedetomidine Withdrawal in Critically Ill Pediatric Patients

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OBJECTIVES This study describes our experience with a clonidine transition protocol to prevent dexmedetomidine (DEX) withdrawal in critically ill pediatric patients.

METHODS Retrospective review of electronic medical records of patients in the pediatric intensive care unit of a single tertiary children's hospital. All patients up to 19 years of age, who received concomitant DEX infusion and enteral clonidine between June 1, 2016, and May 31, 2018, were included.

RESULTS Two of 24 encounters had DEX restarted for withdrawal (8.3%). Five of 14 encounters who were transitioned to clonidine 2 mcg/kg every 6 hours required an increased dose, and 1 of 10 encounters transitioned to clonidine 4 mcg/kg every 6 hours required an increased dose (36% vs 10%, $p = 0.21$). For encounters with clonidine dose increases, 5 of 6 had improvements in Withdrawal Assessment Tool-1 (WAT-1) scores. Of these 5 encounters, 4 had decreasing or stable opioid and sedative requirements and 1 was transitioned to methadone. No encounters required discontinuation of clonidine owing to adverse events. Two of 24 encounters met our safety endpoint. One received a fluid bolus during the clonidine transition with no change in clonidine dosing, while the other had clonidine dose decreased for asymptomatic bradycardia.

CONCLUSIONS The 24 encounters in our retrospective study add to the limited literature available to describe dosing, initiation time, and duration of clonidine to prevent withdrawal from DEX in critically ill pediatric patients. Further research is needed to clarify the optimal dosing and duration of clonidine to prevent DEX withdrawal in pediatric patients.

ABBREVIATIONS DEX, dexmedetomidine; ICU, intensive care unit; IV, intravenous; PICU, pediatric intensive care unit; WAT-1, Withdrawal Assessment Tool-1

KEYWORDS clonidine; critical care; dexmedetomidine; pediatric; pediatric intensive care unit; sedatives; withdrawal

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Introduction

Dexmedetomidine (DEX) is increasingly used as a continuously infused sedative in mechanically ventilated pediatric patients and is considered by some to be a first-line sedation agent in the pediatric intensive care unit (PICU).^{1,2} In the PICU at our institution, DEX infusion is initiated, without bolus, at 0.3 mcg/kg/hr and can be titrated to a maximum dose of 2 mcg/kg/hr. DEX has numerous advantages as a sedative, including ease of titratability and use without regard to ventilation status.^{3,4} In addition, the use of DEX is associated with opioid- and benzodiazepine-sparing effects, lower delirium risk, decreased duration of mechanical ventilation, and shorter stay in PICU.^{5–8}

Prolonged administration of DEX is associated with withdrawal symptoms when it is discontinued abruptly or weaned expeditiously. This withdrawal effect, char-

acterized by agitation, hypertension, and tachycardia, has been observed in our PICU and described in previous studies.^{9–13} Burbano et al⁹ observed that 27% of patients experienced agitation and tachycardia and 35% experienced hypertension; these withdrawal signs occurred at more than twice the rate among those for whom DEX was discontinued abruptly. Haenecour et al¹² found a 35% incidence of DEX withdrawal in children after receiving infusions longer than 48 hours. Similarly, Whalen et al¹³ described a 30% incidence of DEX withdrawal after prolonged infusion (>48 hours) in children. Withdrawal symptoms may result in significant distress for patients and families, prolonged length of stay, and significant health care costs.^{14–16}

One strategy used to prevent withdrawal symptoms is to taper DEX. At our institution, DEX may only be administered in the PICU or procedural areas; hence, a tapering approach may increase the length of stay

in the PICU.

An alternative strategy to prevent DEX withdrawal symptoms involves transitioning DEX to enteral clonidine, another α -2 agonist.^{17–20} Clonidine has been used to prevent and treat withdrawal symptoms associated with several classes of drugs including opioids, alcohol, and nicotine.^{15,21–23} It also provides adequate sedation for patients in the PICU and is well tolerated.^{24–33} Clonidine has excellent oral bioavailability, which makes it a convenient medication for enteral administration. Likewise, its longer half-life (i.e., 8 to 12 hours) enables it to be given daily.³⁴ Clonidine also has a lower drug acquisition cost than DEX.^{35,36}

To the best of our knowledge, 3 retrospective studies^{12,19,20} have examined the use of a clonidine transition strategy to prevent DEX withdrawal in pediatric patients. Only one of these studies has described a clonidine dosing strategy.¹⁹ Recently, Thompson et al³⁷ surveyed the members of the American Academy of Pediatrics Section on Critical Care and found that most respondents were managing DEX withdrawal symptoms via a regimented wean of DEX and concurrent initiation of clonidine. The clonidine dosing was variable, but the most common regimen was enteral clonidine at starting dose of 1 mcg/kg every 6 hours.³⁷ Currently, there are limited data regarding optimal dosing and duration of clonidine to mitigate DEX withdrawal.

Beginning in 2016, a DEX weaning protocol, which incorporated a clonidine transition, was implemented in our PICU. In this study, we report our experience with a clonidine transition protocol to prevent symptoms of DEX withdrawal.

Materials and Methods

This was a retrospective, single-center study evaluating the effect of enteral clonidine on DEX withdrawal symptoms in pediatric patients who received concomitant DEX infusion. The electronic medical records (EPIC Systems, Verona, WI) of patients admitted to the Barbara Bush Children's Hospital Pediatric Intensive Care Unit at Maine Medical Center between June 1, 2016, and May 31, 2018, were reviewed for use of DEX and clonidine treatment courses. An initial search identified patients who received enteral clonidine to prevent DEX withdrawal during the study period. All patients ≤ 19 years of age who received concomitant continuous infusion DEX and enteral clonidine per protocol, and were admitted to the PICU, were eligible for inclusion. Patients who received DEX for < 48 hours were excluded. Patients were also excluded if we were unable to assess information within 24 hours after DEX was discontinued, which included those who were discharged during the assessment period. Study data were collected and managed by using Research Electronic Data Capture (REDCap) hosted at Tufts University.^{38,39} One study investigator (JL) collected and entered data into REDCap. Other study investigators (JM, JB) evalu-

ated a sample of the data for errors and discrepancies.

Data were collected and analyzed in 5 defined phases: 1) the DEX baseline phase included the 24 hours preceding the first clonidine dose; 2) the clonidine transition phase started with the first dose of clonidine and continued until DEX was discontinued; 3) the clonidine maintenance phase began when DEX was stopped and continued until clonidine tapering was started; 4) the clonidine taper phase began when clonidine dosing frequency was reduced until discontinuation; and 5) the post α -2 agonist phase included the 24-hours following clonidine discontinuation.

Per protocol, clonidine was initiated if the duration of DEX was ≥ 72 hours or earlier at the discretion of the treating physician. The dose of clonidine was 2 mcg/kg every 6 hours for patients < 6 months of age and 4 mcg/kg every 6 hours for patients ≥ 6 months of age. There were no formal hold parameters for clonidine, as patients were presumably tolerating the hemodynamic effects of DEX. Per protocol, DEX dose rate was decreased by 50%, 30 minutes after the second dose of clonidine, and DEX was discontinued 30 minutes after the third dose of clonidine.

Weaning of clonidine and other sedatives could occur simultaneously, though generally clonidine dosing was maintained until after extubation and weaning of other agents occurred. The exact weaning approach for other sedatives was adjudicated on a case by case basis, but generally opioids and benzodiazepines were weaned 10% to 20% daily over a period of 5 to 10 days by duration of exposure and patient withdrawal symptoms (e.g., tremors, sweating).^{40–42} Clonidine was weaned as follows: 4 mcg/kg/dose every 6 hours for 4 doses, then 4 mcg/kg/dose every 8 hours for 3 doses, then 4 mcg/kg/dose every 12 hours for 2 doses, and finally 4 mcg/kg at 24 hours for 1 dose. The clonidine dosing protocol was developed by our pediatric pharmacists and pediatric intensive care physicians, based on developmental pharmacokinetics and extrapolation from previous publications in adults and children.^{18,27–31,33,43–45}

Many different definitions of DEX withdrawal have been reported in the literature.^{9–13,19,20} We defined DEX withdrawal as the need to restart DEX within 24 hours following its discontinuation. We also evaluated Withdrawal Assessment Tool-1 (WAT-1) scores,^{46,47} the incidence of patients with WAT-1 scores ≥ 3 , and the incidence of clonidine dose increase. State Behavioral Scale (SBS) scores⁴⁸ were also collected for those with DEX restart or clonidine dose increase. Outcomes to assess safety included occurrence of hypotension or bradycardia requiring intervention. We defined hypotension and bradycardia as blood pressure or heart rate less than fifth percentile for age. Interventions for these included a fluid bolus, holding or decreasing α -2 agonist dose, and initiation or dose increases of vasoactive medications. Dexmedetomidine duration and cumulative dose were calculated from initiation until the first

Table 1. Benzodiazepines and Morphine Conversion Equivalents^{49–51}

Drug	Equivalents
1 mg of IV lorazepam	
Midazolam	3 mg (IV)
Clonazepam	0.25 mg (oral)
Diazepam	5 mg (IV)
Chlordiazepoxide	10 mg
10 mg IV morphine	
Oxycodone	20 mg (oral)
Fentanyl	100 mcg (IV)
Hydromorphone	1.5 mg (IV)
Hydromorphone	7.5 mg (oral)

dose of clonidine. Evaluation of opioid and sedative requirements included doses of morphine, oxycodone, hydromorphone, fentanyl, methadone, lorazepam, midazolam, and phenobarbital. All benzodiazepines administered were converted to lorazepam equivalents and all opioids administered were converted to morphine equivalents except methadone (Table 1).^{49–51} We compared total sedative requirements across transition phases as an average per 24 hours to take into account variable duration of the phases. Descriptive statistics were presented as median (interquartile range) or median (range). Categorical variables were compared between groups by using the Fisher exact test. Continuous variables were compared between groups by using the Mann-Whitney *U* test. By convention, $p < 0.05$ was considered statistically significant. Rates of safety events were calculated and corresponding 95% confidence intervals were generated by using the binomial distribution method.

Results

A total of 28 patients were screened for eligibility. Six patients were excluded from the study, 2 of whom were transferred to another hospital during DEX to clonidine transition, 2 had received DEX for <48 hours, 1 did not follow the clonidine protocol, and 1 was discharged to home before clonidine taper was completed. Of the 22 patients included, 1 patient received 3 separate courses of concomitant DEX and clonidine. Another patient received 2 separate courses of concomitant DEX and clonidine, although only 1 course was included in the analysis owing to clonidine protocol deviation; thus, there were 24 DEX-to-clonidine encounters.

The median age was 3.5 months (IQR, 2–28.5). The median duration of mechanical ventilation was 6 days (IQR, 3–12). The median ICU length of stay was 11.5 days (IQR, 6.75–15). The median duration of DEX was 3.8 days (IQR, 2.9–5.7) and the median cumulative DEX dose was 120.6 mcg/kg (IQR, 65.7–152.8). The median

Table 2. Demographics

Demographic	Result*
Age, mo	3.5 (2, 28.5)
Male, n (%)	16 (62.5)
Race, n (%)	
Caucasian	19 (79.2)
African American	3 (12.5)
Other	2 (8.3)
Admission diagnosis, n (%)	
Respiratory failure/distress	11 (45.8)
Postoperative congenital heart disease	10 (41.6)
Septic shock	1 (4.2)
Other	2 (8.4)
Duration of ventilation, days	6 (3, 12)
PICU LOS, days	11.5 (6.75, 15)
Cumulative DEX dose, mcg/kg	120.6 (65.7, 152.8)
Maximum DEX dose, mcg/kg/hr	1.65 (1.4, 2.0)
Median hourly DEX dose, mcg/kg/hr	1.2 (0.87, 1.50)
DEX treatment duration, days	3.8 (2.9, 5.7)
DEX wean duration, hr	7 (6, 13.2)

DEX, dexmedetomidine; LOS, length of stay; PICU, pediatric intensive care unit

* Continuous data reported as median (Q1, Q3). Data available for all 24 encounters.

hourly DEX dose was 1.2 mcg/kg/hr (IQR, 0.87–1.50) and the median maximum DEX dose per patient was 1.65 mcg/kg/hr (IQR, 1.4–2.0) (Table 2).

All 24 encounters received clonidine enterally, in either oral suspension or tablet formulation. They were initiated on clonidine at an interval of every 6 hours per the protocol. Clonidine was continued for a median of 18.2 hours (IQR, 12.5–21.6) before DEX discontinuation. The median clonidine weaning duration was 57.6 hours (IQR, 44.9–68.2) for a median total clonidine treatment duration of 4.7 days (IQR, 4–6.9) (Table 3).

Two encounters in our cohort had DEX restarted and 6 encounters had clonidine dose increased. Of these encounters, 1 had DEX restarted and clonidine dose increased at the same time. Of the 2 encounters that had DEX restarted, 1 had received 2 mcg/kg every 6 hours and 1 had received 4 mcg/kg every 6 hours. Of the 6 encounters that had clonidine dose increases, 5 had received 2 mcg/kg every 6 hours and 1 had received 4 mcg/kg every 6 hours.

The median cumulative DEX dose was 253 mcg/kg (IQR, 245–261) in the DEX restart group and the median cumulative DEX dose was 117 mcg/kg (IQR, 61.2–141) in the no DEX restart group ($p = 0.06$). The median highest WAT-1 scores were not significantly different between the DEX restart and no DEX restart groups ($p =$

Table 3. Clonidine Characteristics

Characteristic	Result*
Initial clonidine frequency q 6 hr, n (%)	24 (100)
Initial clonidine dose, n (%)	
2 mcg/kg	14 (58.3)
4 mcg/kg	10 (41.7)
Clonidine treatment duration, days	4.7 (4, 6.9)
DEX and clonidine overlap duration, hr	18.2 (12.5, 21.6)
Clonidine wean duration, hr	57.6 (44.88, 68.16)

DEX, dexmedetomidine; q, every

* Continuous data reported as median (Q1, Q3). Data available for all 24 encounters.

0.27). In the clonidine dose increase group, the median cumulative DEX dose was 111 mcg/kg (IQR, 76.9–207) compared to 124 mcg/kg (IQR, 62.5–151) in the no clonidine increase group ($p = 0.93$). There was a significant difference in the median highest WAT-1 scores between the clonidine dose increase group and the no clonidine increase groups ($p = 0.01$) (Tables 4 and 5).

WAT-1 scores were evaluable for all transition phases (Table 6). The median highest WAT-1 scores by phase were as follows: DEX baseline 1.5, clonidine transition 1.5, clonidine maintenance 4, clonidine taper 3, and post α -2 agonist phase 1. Opioid and sedative requirements decreased in each subsequent transition phase (Table 6).

Two encounters experienced bradycardia or hypotension that required interventions, for an overall rate of 8% (95% CI, 1–25). One patient diagnosed with septic shock received a dopamine infusion and an albumin bolus during the DEX baseline phase (prior to the first dose of clonidine). The dopamine infusion was stopped, and a second albumin bolus was given during the clonidine transition phase. Another patient experienced asymptomatic bradycardia from the DEX baseline phase through hospital discharge, for which

the treatment team decreased the clonidine dose from 0.4 mg/dose to 0.3 mg/dose in the clonidine maintenance phase.

In a post hoc analysis, the median WAT-1 and SBS scores, and opioid and sedative requirements, were compared before and after each time DEX was restarted and/or clonidine dose was increased (Tables 7 and 8). Of the 2 encounters that had DEX restarted, 1 encounter's median WAT-1 scores decreased from 2.5 to 0 and the other's decreased from 4 to 1. Of the 6 encounters that had clonidine dose increased, 5 had a decrease in median WAT-1 scores after clonidine dose escalation without increasing opioid and sedative doses and similar or improved SBS scores.

Discussion

We found an 8.3% rate of clinically significant withdrawal in our cohort, defined by the incidence of restarting a DEX infusion. There is currently no consensus definition for DEX withdrawal. DEX withdrawal has been based on retrospective chart reviews with investigator assessment of withdrawal; non-specific measures such as hypertension and tachycardia; or by WAT-1 scores, which have not been validated for DEX withdrawal.^{12,19,20} Our definition is practical, as clinicians who make the decision to restart DEX would have considered the presence of withdrawal symptoms such as agitation, hypertension, tachycardia, and elevated WAT-1 scores. Since DEX may only be administered in the ICU at our institution, DEX restart and taper due to withdrawal symptoms may increase PICU length of stay, prevent transfer to other units, and increase drug costs.³⁶ We suggest that it is more meaningful to use restarting DEX as an objective measure of clinically significant withdrawal. The 2 encounters for whom DEX was restarted had larger cumulative DEX doses, a previously identified risk factor for DEX withdrawal,^{12,19} and higher WAT-1 scores than those without intervention. Further support for this definition can be seen by WAT-1 score improve-

Table 4. Comparison Between Dexmedetomidine Restart Group vs No Dexmedetomidine Restart Group

	DEX		p value
	Restart (n = 2)	No Restart (n = 22)	
Clonidine dosing group			
2 mcg/kg	1	13	1
4 mcg/kg	1	9	
Cumulative DEX dose, mcg/kg*	253 (245, 261)	117 (61.2, 141)	0.06
Duration of DEX, days*	19 (12.7, 25.2)	3.6 (2.8, 5.4)	0.04
Highest WAT-1 score*,†	7 (7, 7)	4.5 (1.25, 6.75)‡	0.27
Elevated WAT-1 score (≥ 3)*	2 (100%)	14 (66%)‡	1

DEX, dexmedetomidine; WAT-1, Withdrawal Assessment Tool-1

* Continuous data reported as median (Q1, Q3).

† From initiation to 24 hours after discontinuation of clonidine.

‡ WAT-1 scores were not collected in 2 patient encounters; therefore, evaluable WAT-1 scores were available in 21 of the 22 patient encounters.

Table 5. Comparison Between Clonidine Dose Increase Group vs No Clonidine Dose Increase Group

	Clonidine		p value
	Dose Increase (n = 6)	No Dose Increase (n = 18)	
Clonidine dosing group			
2 mcg/kg	5	9	0.21
4 mcg/kg	1	9	
Cumulative DEX dose, mcg/kg*	111 (76.9, 207)	124 (62.5, 151)	0.92
Duration of DEX, days*	3 (2.9, 4.8)	3.8 (2.9, 5.9)	0.58
Highest WAT-1 score*, †	7.5 (6.25, 8.75)	3 (1, 6)‡	0.01
Elevated WAT-1 score (≥3)	6 (100%)	10 (59%)‡	0.12

DEX, dexmedetomidine; WAT-1, Withdrawal Assessment Tool-1

* Continuous data reported as median (Q1, Q3).

† From initiation to 24 hours after discontinuation of clonidine.

‡ WAT-1 scores were not collected in 1 patient encounter; therefore, evaluable WAT-1 scores were available in 17 of the 18 patient encounters.

ment in the 48 hours following restarting DEX. These 2 encounters had either stable or decreasing opioid and sedative requirements after intervention, although α -2 agonists such as clonidine and DEX may also mitigate withdrawal from opioids and other sedatives.^{15,52}

We were able to manage elevated WAT-1 scores in 6 encounters with the use of increased clonidine dose without restarting DEX infusion. The most common clonidine dose escalation was from 2 mcg/kg every 6 hours to 4 mcg/kg every 6 hours. After clonidine dose

escalation, the median WAT-1 scores improved in 5 of 6 encounters. One encounter had increased opioid requirements, and another was transitioned to methadone. For the remaining encounters, an increased dose of clonidine treated DEX withdrawal, as demonstrated by improvements in WAT-1 scores, despite stable or decreasing opioid and sedative doses. Additionally, for those encounters with SBS scores, values improved or were unchanged, suggesting the absence of rebound agitation. There are limited data on the optimal cloni-

Table 6. Transition Phases*

Variable	Phase				
	DEX Baseline	Clonidine Transition	Clonidine Maintenance	Clonidine Taper	Post α -2 Agonist
Evaluable, n (%)	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)
Phase duration, hr	24 (24, 24)	18.2 (12.5, 21.7)	29.5 (21.3, 73.4)	60.3 (44.5, 75.9)	24 (24, 24)
Elevated WAT-1 score, n (%)†	4 (16)	6 (25)	12 (50)	8 (33)	1 (4)
Median highest WAT-1 scores	1.5	1.5	4	3	1
Opioid, n (%)‡	16 (66)	14 (58)	12 (50)	4 (17)	2 (8)
Morphine equivalents, mg/kg/24 hr§	0.32 (0.19, 0.97)	0.24 (0.12, 0.27)	0.17 (0.06, 0.28)	0.08 (0.02, 0.16)	0.3 (0.17, 0.43)
Benzodiazepine, No. (%)¶	13 (50)	8 (33)	7 (27)	2 (8)	1 (4)
Lorazepam equivalents, mg/kg/24 hr†	0.33 (0.1, 0.38)	0.09 (0.04, 0.15)	0.05 (0.03, 0.14)	0.33 (0.3, 0.37)	0.21 (0.21, 0.21)
Methadone, No. (%)	1 (4)	1 (4)	2 (8)	0 (0)	0 (0)
Phenobarbital, No. (%)	1 (4)	0 (0)	1 (4)	1 (4)	1 (4)

DEX, dexmedetomidine; WAT-1, Withdrawal Assessment Tool-1

* Continuous data reported as median (Q1, Q3).

† Elevated WAT-1 score is defined as score ≥ 3 .

‡ Morphine, oxycodone, hydromorphone, or fentanyl.

§ Only for those patients who received an opioid, or benzodiazepine.

¶ Lorazepam, or midazolam.

Table 7. Dexmedetomidine Restart Group*

DEX Restart	WAT-1 Scores 48 hr Before/ After DEX Restart	Cumulative DEX Dose, mcg/kg	DEX Treatment Duration Prior to Initiation of Clonidine, days	SBS Scores 48 hr Before/ After DEX Restart	Opioids 48 hr Before/ After DEX Restart, IV Morphine Equivalents, mg/kg/24 hr	Benzodiazepines 48 hr Before/After DEX Restart, IV Lorazepam Equivalents, mg/kg/24 hr	Methadone 48 hr Before/After DEX Restart, mg/kg/24 hr	Phenobarbital 48 hr Before/After DEX Restart, mg/ kg/24 hr
Patient 1		270	32					
Before	2.5 (1, 7)			0	0	0	0.05	0
After	0 (1, 7)			NC	0	0	0.06	0
Patient 2†		236	6.5					
Before	4 (0, 7)			1 (0, 1)	0.15	0.53	0	0
After	1 (0, 7)			0 (-1, 1)	0.05	0.22	0	0

DEX, dexmedetomidine; NC, not collected; WAT-1, Withdrawal Assessment Tool-1

* Continuous data reported as median (min, max).

† Patient had concomitant dexmedetomidine restart and clonidine dose increase.

dine dose and frequency to prevent DEX withdrawal, which has led to institutional variation as reported recently in a questionnaire by Thompson et al.³⁷ Although the clonidine dosing was variable, enteral clonidine at a starting dose of 1 mcg/kg at an interval of every 6 hours was the most common regimen reported.³⁷ While not meeting the conventional threshold for statistical significance, we observed that more encounters that received 2 mcg/kg every 6 hours had their clonidine dose increased than those that received 4 mcg/kg every 6 hours. Based on our experience, the 1 mcg/kg every 6 hours dosing frequently used in other institutions may be insufficient. Others have also suggested higher clonidine doses for this indication at 3 to 5 mcg/kg every 8 hours.^{18,19} As our cohort has high cumulative DEX doses,^{3,13,19} perhaps a higher clonidine dose would not be necessary for encounters receiving smaller DEX doses. While one could consider this approach, our data do not support it as we observed similar DEX doses among encounters with and without clonidine dose increases. Similarly, an argument could be made in favor of the 2-mcg/kg dose given that dose escalation only occurred in 36% of the cohort exposed to this dose. We believe that this is an unacceptable rate of intervention, as DEX withdrawal has been noted to occur among 27% to 35% of patients after prolonged infusion^{9,12,13} and withdrawal symptoms improved with the increased clonidine dose. A prospective study with a larger sample size is needed to determine the appropriate dose of clonidine for this indication.

We observed 2 patients who developed bradycardia or hypotension requiring intervention. One patient diagnosed with septic shock received an albumin bolus before and another albumin bolus during the clonidine transition phase. We cannot exclude the possibility that clonidine may have contributed to the hypotension that the patient experienced during the clonidine transition phase although septic shock was likely the reason for the patient's hemodynamic instability. Another patient had asymptomatic bradycardia that began during DEX infusion and persisted during the clonidine transition. Owing to persistent asymptomatic bradycardia, the treatment team decreased the clonidine dose. Bradycardia remained stable in the next 48 hours, and patient was discharged to a rehabilitation facility. No patient in our cohort required clonidine discontinuation secondary to bradycardia or hypotension. However, owing to the small sample and wide confidence intervals we cannot exclude the possibility that this could occur at a rate of up to 25%.

Our study has some important limitations. WAT-1 scores of 3 or greater as a sign of withdrawal was validated for monitoring opioid and benzodiazepine withdrawal in pediatric patients.^{46,47} Use of WAT-1 has not been validated for assessment of DEX withdrawal, as only 37% of the cohort received DEX in the validation study, and important factors such as cumulative

Table 8. Clonidine Dose Increase Group

Clonidine Dose Increase	Median WAT-1 Scores 48 hr Before/After Clonidine Dose Increase*	Clonidine Dose Escalation	Cumulative DEX Dose, mcg/kg	DEX Treatment Duration Prior to Initiation of Clonidine, days	SBS Scores 48 hr Before/After Clonidine Dose Increase*	Opioids 48 hr Before/After Clonidine Dose Increase, IV Morphine Equivalents, mg/kg/24 hr	Benzodiazepines 48 hr Before/After Clonidine Dose Increase, IV Lorazepam Equivalents, mg/kg/24 hr	Methadone 48 hr Before/After Clonidine Dose Increase, mg/kg/24 hr	Phenobarbital 48 hr Before/After Clonidine Dose Increase, mg/kg/24 hr
Patient 1		2 mcg/kg q 6 hr increased to 4 mcg/kg q 6 hr	118.3	2.8					
Before	8 (1,10)				-0.5 (1, 1)	0.12	0	0	0
After	2.5 (1, 9)				NC	0.02	0	0	0
Patient 2		2 mcg/kg q 6 hr increased to 2.5 mcg/kg q 6 hr	37	2.9					
Before	4 (0, 9)				0.5 (0, 1)	0.19	0	0	0
After	1.5 (0, 9)				0 (0, 0)	0	0	0.33	0
Patient 3		2 mcg/kg q 6 hr increased to 5 mcg/kg q 6 hr	104	3					
Before	6 (3, 7)				0 (-1, 2)	0.16	0	0	0
After	2 (0, 8)				0 (0, 0)	0.16	0	0	0
Patient 4		2 mcg/kg q 6 hr increased to 4 mcg/kg q 6 hr	236	5.3					
Before	4 (2, 6)				NC	0.08	0	0	0
After	2 (0, 6)				NC	0	0	0	0
Patient 5		2 mcg/kg q 6 hr increased to 3 mcg/kg q 6 hr	67.9	3					
Before	1 (0, 6)				0 (-1, 1)	0.3	0.01	0	0.33
After	1 (0, 3)				-1 (-1, 1)	0.59	0	0	0.22
Patient 6†		4 mcg/kg q 6 hr increased to 4 mcg/kg q 4 hr	236	6.5					
Before	4 (0, 7)				1 (0, 1)	0.15	0.53	0	0
After	1 (0, 7)				0 (-1, 1)	0.05	0.22	0	0

DEX, dexmedetomidine; NC, not collected; q, every; WAT-1, Withdrawal Assessment Tool-1

* Continuous data reported as median (min, max).

† Patient had concomitant dexmedetomidine restart and clonidine dose increase.

dose and duration were not reported.^{46,47} Lardieri et al²⁰ previously used WAT-1 score as a measure of DEX withdrawal in their evaluation of transdermal clonidine. Shutes et al¹⁹ critique WAT-1 as it does not include components associated with α_2 -adrenergic withdrawal, such as tachycardia and hypertension. They advocated for the development of a specific central α_2 -adrenergic receptor agonist withdrawal scoring tool.¹⁹ We share the same concern that WAT-1 score may not be a sensitive and specific indicator for DEX withdrawal. In our cohort, WAT-1 scores were frequently above the threshold of 3 in the no-intervention group, so it is unclear whether a WAT-1 score of ≥ 3 is suggestive of DEX withdrawal. However, we cannot exclude the possibility that elevated WAT-1 scores were also due to weaning or potentially withdrawal from opioids and benzodiazepines. The highest WAT-1 scores for the 2 encounters that had DEX restarted were both 7. This may suggest that a higher threshold WAT-1 score may indicate DEX withdrawal or simply that it is difficult to identify the causative agent when patients experiencing withdrawal are weaned from multiple sedatives and analgesics at one time. However, the decrease in WAT-1 score upon restarting DEX may suggest α_2 withdrawal, especially in the setting of decreasing or stable opioids and sedative doses. Further studies are needed to assess the utility of WAT-1 for DEX withdrawal or establish alternate assessment methods.

We were susceptible to potential inaccurate documentation in the electronic medical record given that this was a retrospective study. Similar to prior studies, we acknowledge that the overlap of opioids and benzodiazepines could have contributed to the withdrawal symptoms observed. This reflects the challenges that clinicians face in practice when diagnosing and managing withdrawal with multiple analgesics and sedatives are involved.¹² Although we observed a decrease in median WAT-1 scores after restarting DEX and increasing clonidine dose, we cannot exclude the possibility that concurrent opioids and benzodiazepines may have contributed to such improvement, although most had decreasing or stable opioids and sedative doses. We had a small sample size, which limits our ability to conclude that clonidine transition is a safe intervention. We did not have a comparator group, which limits our ability to conclude that clonidine transition is effective. We did not report changes in vital signs owing to inconsistent documentation and missing data at certain time points. Our study represents a small single-center experience, which makes our data potentially subject to type II errors and lowers the precision of our estimates. However, our study comprised the second largest sample size currently in the literature, investigating the prophylactic use of clonidine for DEX withdrawal. The largest study was conducted by Haenecour et al¹² in 2017, who reported on 37 patients who received

prophylactic clonidine after at least 48 hours of DEX exposure. Our study differed from that of Haenecour et al¹² by using a standard dosing protocol, thereby minimizing the variability in the approach of transitioning patients.

Conclusion

The 24 encounters in our retrospective study add to the limited literature available to describe dosing, initiation time, and duration of clonidine to prevent withdrawal from DEX in critically ill pediatric patients. Though not statistically significant, we observed that more encounters that received an initial dose of 2 mcg/kg every 6 hours required an increased dose than those that received an initial dose of 4 mcg/kg every 6 hours, with a corresponding reduction in subsequent WAT-1 scores. This suggests that a clonidine dosing regimen of 1 mcg/kg every 6 hours that is commonly used at many institutions, based on a recent survey, may be insufficient to manage DEX withdrawal. The experiences gained from this study will be used to improve our existing clonidine transition protocol including a standardized 4 mcg/kg initial dose for all patients receiving prophylactic clonidine. Further research is needed to clarify the optimal dosing and duration of clonidine to prevent DEX withdrawal within the PICU.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees. Given the nature of the study, the committee waived HIPAA authorization, patient assent, and parental permission.

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