Prevention of Withdrawal in Pediatric Patients Receiving Long-term Dexmedetomidine Infusions

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OBJECTIVE Determine if the addition of clonidine was associated with a decreased incidence of dexmedetomidine withdrawal in patients who received prolonged dexmedetomidine infusions.

METHODS This was a retrospective observational cohort study conducted at a single-center PICU in an academic children's hospital. Children 1 month to 18 years of age who received dexmedetomidine infusion for 5 days or longer were included in the study.

RESULTS Fifty patients met the inclusion criteria with 15 patients who received clonidine and 35 who received a dexmedetomidine wean alone. Withdrawal criteria included blood pressure changes, heart rate changes, and documented agitation. Overall, there was no difference in change in blood pressure or documented agitation between groups. Patients who did not receive clonidine had a greater number of heart rate readings above normal for age following discontinuation of the infusion, yet this was not statistically significant. Potentially more importantly, the addition of clonidine did not impact the duration of dexmedetomidine wean or the PICU length of stay after dexmedetomidine discontinuation.

CONCLUSIONS The addition of clonidine while weaning a long-term dexmedetomidine infusion did not lead to lower blood pressures or agitation, but did lead to decreased percentage of heart rates above the age-appropriate range. The clinical significance of this is unknown, and further investigation is warranted. The addition of clonidine did not decrease time to weaning off dexmedetomidine or shorten PICU length of stay.

ABBREVIATIONS EMR, electronic medical record; ICU, intensive care unit; PICU, pediatric intensive care unit; WAT-1, Withdrawal Assessment Tool

KEYWORDS adrenergic alpha-2 receptor agonists; child; clonidine; critical care; dexmedetomidine; withdrawal

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Introduction

Sedation is frequently required for children who are critically ill and requiring mechanical ventilation. To maintain goal levels of sedation in children, physicians often use intermittent dosing or continuous infusions of benzodiazepines and opioids.¹ In recent years, the use of dexmedetomidine as a primary and secondary sedative has increased.¹ Dexmedetomidine (Precedex, Hospira Worldwide, Lake Forrest, IL) is an α_2 -adrenergic agonist chemically related to clonidine.^{2,3} Both dexmedetomidine and clonidine exhibit their sedative effects by decreasing the release of noradrenaline in the sympathetic nerve endings and thereby decreasing the firing at the locus coeruleus in the brainstem.^{2,3} Dexmedetomidine is only available intravenously, while clonidine can be given enterally or transdermally.

Given the increased use, several recent studies have examined the frequency of withdrawal in pediatric patients who received a continuous dexmedetomidine infusion.^{3–7} Although no formal definition for dexmedetomidine withdrawal exists, previous studies consistently recognize the symptoms of tachycardia,

hypotension, and/or agitation after the cessation of dexmedetomidine as symptoms of withdrawal. Of note, the median duration of dexmedetomidine infusion in many prior studies is less than 72 hours.^{3–5} Whelan et al⁶ reported a median duration of dexmedetomidine use of 141 hours and found that 30% of patients had withdrawal symptoms.⁶ Similarly, Haenecour et al⁷ reported a duration use of 124.3 hours and found that 35% of patients experienced withdrawal. Because clonidine has a similar effect to dexmedetomidine on the α_2 -adrenergic receptors and can be administered through several routes, it is well suited as an alternative to weaning the continuous infusion of dexmedetomidine. This could potentially reduce patient time in the PICU in centers where dexmedetomidine usage is not allowed on the general wards. It could also reduce the duration of central intravenous access. This concept is in line with the current practice for weaning opioids and benzodiazepines with the addition of long-acting oral agents.

There is currently no consensus on how to wean dexmedetomidine infusions to prevent withdrawal, but

Table 1. Baseline Patient Demographics

Characteristic	Clonidine Cohort (n = 15)	No Clonidine Cohort (n = 35)	p value
Age, median (IQR), yr	2 (1.25–4)	2 (0.92–7)	0.958
Sex, female, n (%)	7 (46.7)	13 (37)	0.546
Weight, median (IQR), kg	12.3 (9.4–20)	12.5 (9.3–24.4)	0.816
Admitting diagnosis, n (%)			
Respiratory	5 (33.3)	17 (48.6)	0.367
Trauma	2 (13.3)	6 (17.1)	1
Surgical	1 (6.7)	7 (20)	0.407
Other	7 (46.7)	5 (14.3)	0.181

2 potential methods include weaning the drip over 24 to 72 hours or converting patients to enteral or transdermal clonidine then quickly weaning the dexmedetomidine infusion (typically over 24 hours) followed by a slow wean of clonidine. Of note, no validated protocol exists for either method.

As the use of dexmedetomidine in pediatric patients who are critically ill increases and it is being used for longer periods, it is important to evaluate the best method to prevent withdrawal upon discontinuing dexmedetomidine. In this study, we compare 2 different methods used in the PICU to prevent withdrawal following a long-term infusion of dexmedetomidine.

Materials and Methods

Patient Population. The Institutional Review Board approved this retrospective pragmatic study evaluating the incidence of withdrawal from dexmedetomidine associated with 2 distinct clinical practices for weaning: 1) weaning of dexmedetomidine infusion alone, or 2) weaning of dexmedetomidine infusion with the addition of clonidine. The use of clonidine was not protocolized and was used per clinician's discretion. This study took place at a large academic medical center with a 36-bed PICU from July 1, 2015, to June 31, 2017. Patients aged 1 month to 18 years were included in this study if they received a dexmedetomidine infusion for 5 days or longer (Table 1). Patients were excluded from the study if their heart rate or blood pressure was not documented at least 6 times per day, the patient had been previously treated with dexmedetomidine or clonidine at a referring hospital, clonidine was a home medication for the patient, or if the patient received any inotropic medications, chronotropic medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta blockers during the weaning phase.

Of note, during the study period our institution did not have a standardized protocol for dexmedetomidine weaning or clonidine usage, and the weaning strategy was left to the discretion of the attending physician with input from the clinical pharmacy specialist. Patients were assigned to these retrospective groups by the

presence or absence of clonidine, but the dose, rate, and length of wean varied. Initially as dexmedetomidine began being used for prolonged periods of sedation, patients receiving infusions for >3 to 5 days were transitioned to clonidine, but as evidence emerged showing that dexmedetomidine could be successfully weaned even after 5 days of therapy without the addition of clonidine,⁷ many clinicians started to feel more comfortable with slowly titrating off a dexmedetomidine infusion and did not add clonidine. When clonidine was used, it was typically initiated 1 to 2 days prior to anticipation of discontinuing dexmedetomidine infusion at a dose of 5 to 10 mcg/kg/day. When dexmedetomidine was weaned without the addition of clonidine, a standing wean order would be placed during daily morning rounds. The infusion would be weaned by 0.2 µg/kg/hr every 6 to 12 hours depending on the patient's current ventilator settings and readiness for extubation. It was also not uncommon for patients to be extubated when receiving doses of dexmedetomidine of 0.4 mcg/kg/hr or less. In this study, we retrospectively evaluate these 2 methods.

Data Collection. Age, sex, weight, admitting diagnosis, and medications prior to admission to our PICU were recorded. To assess for physiological changes during the weaning phase, blood pressure changes, heart rate changes, and the incidence of agitation were documented from chart review. Heart rates and blood pressures were considered elevated if they were above our standard alarm parameters for age. These alarm parameters are based off standard age and sex reference ranges embedded within the EMR. Each day was measured as a 24-hour period starting with midnight (12:00 am to 11:59 pm). Baseline blood pressures and heart rates were measured on the day prior to dexmedetomidine discontinuation (day -1). On the day of dexmedetomidine discontinuation or when the wean was initiated (wean initiation/discontinuation day), neither blood pressures nor heart rates were evaluated. We chose not to record data on this day owing to limitations in determining the exact time course of events retrospectively in our EMR. Postinfusion blood pressures and heart rates were then collected the 2

Table 2. Change in Covariates Between the Cohorts

Outcome	Clonidine Cohort (n = 15)	No Clonidine Cohort (n = 35)	p value
Percentage increase in systolic blood pressure, median (IQR), mm Hg	20 (–18.1 to 31.2)	0 (–13.6 to 16.7)	0.217
Percentage increase in heart rate, median (IQR), bpm	4 (–7 to 10.8)	15 (0–25)	0.045
Agitation documented, n (%)	6 (40)	8 (22.9)	0.304
Max dexmedetomidine rate, median (IQR), mcg/kg/hr	0.8 (0.7–1)	0.9 (0.7–1)	0.853
Dexmedetomidine infusion duration, median (IQR), days	10 (9–15)	8 (7–11)	0.006
Dexmedetomidine wean duration, median (IQR), days	2 (1–2)	2 (1–3)	0.610
ICU length of stay after dexmedetomidine wean initiation, median (IQR), days	3 (1.75–7.5)	3 (1–11)	0.982

days following dexmedetomidine discontinuation (days 1 and 2). The presence of agitation was only collected on days 1 and 2. A patient was considered agitated if the terms *agitation*, *agitated*, or *irritable* appeared in nursing and physician chart documentation. We also examined the duration of overlap with dexmedetomidine and clonidine and PICU length of stay following dexmedetomidine discontinuation between groups. PICU length of stay was determined from the day dexmedetomidine was discontinued and continued until the patient's transfer or discharge orders were placed.

Statistical Analysis. The primary outcome evaluated the difference in blood pressure and heart rate. This was achieved by comparing the percentage of elevated blood pressures on day –1 (the day prior to dexmedetomidine wean initiation) to the percentage of elevated blood pressures on days 1 and 2 (the 2 days after dexmedetomidine wean initiation). This same strategy was used for evaluating heart rate. All data were evaluated with Minitab software, version 7 (Chicago, IL). Categorical data and continuous data were evaluated by the Fisher exact and Mann-Whitney *U* tests, respectively.

Results

Fifty patients met the inclusion criteria: 15 patients who received clonidine and 35 who received a dexmedetomidine wean alone. Of the 15 patients who received clonidine, 13 received enteral clonidine and 2 received transdermal clonidine. The median clonidine dose was 4.5 mcg/kg/day (IQR, 3–9 mcg/kg/day). The median duration of clonidine and dexmedetomidine overlap was 2 days (IQR, 1–3 days). Overall, there was no difference in baseline characteristics between groups. There was no difference in maximum dexmedetomidine infusion rate; however, patients who received clonidine did have a longer total dexmedetomidine infusion duration (Table 2).

There was no significant difference in the percentage of patients who had agitation following dexmedetomidine discontinuation (Table 2). Similarly, there was no increase in the proportion of elevated blood pressures between groups (Figure 1). When evaluating change in heart rate however, the patients in the clonidine group had a greater number of heart rate readings above normal for age following discontinuation of the infusion (Figure 2). The median percentage of elevated blood pressures and heart rates preinfusion and postinfusion discontinuation was also analyzed for both groups (Figures 1 and 2).

There was no significant difference between groups when evaluating the number of days used to wean off the dexmedetomidine infusion (Table 2). For both groups the mean duration was 2 days. Similarly, no difference was seen in length of PICU stay following the initiation of the dexmedetomidine infusion wean (Table 2).

Discussion

As the use of continuous infusion dexmedetomidine has become more prevalent in our PICU, clinicians are seeking to find strategies that ensure efficient weaning of the infusion while minimizing risk of withdrawal and prolonging the need for intensive care. The increased use of dexmedetomidine is not limited to only our institution, as a 2016 systematic review² found 6 randomized controlled trials comparing α_2 -agonists with traditional sedation in pediatrics. Dexmedetomidine had opioid-sparing effects, yet more research is needed.² To our knowledge, this is one of the first studies to evaluate strategies for preventing withdrawal associated with a prolonged (>3 days) continuous infusion of dexmedetomidine.

Each of the 2 weaning strategies evaluated has pros and cons. Weaning the dexmedetomidine infusion without the addition of clonidine is simpler because you are not adding an additional medication. However, many

Figure 1. Percentage of elevated blood pressure before and after discontinuation of dexmedetomidine.

Each dot represents a single patient's blood pressures before and after discontinuation of dexmedetomidine. There was no statistically significant difference between baseline blood pressures of each group ($p = 0.538$), the baseline and post-discontinuation for the clonidine ($p = 0.229$) and no clonidine ($p = 0.529$) group, or the post-blood pressures of each group ($p = 0.320$).

hospitals have policies that may not allow a dexmedetomidine infusion on general pediatric wards; therefore, it is possible this strategy could lengthen PICU length of stay. In contrast, the addition of clonidine to standard sedation in the ICU has been shown to have opioid-sparing effects when used as an adjuvant to standard sedation, so there may be value in adding clonidine while the patient is receiving mechanical ventilation and then weaning once extubated.⁸ The use of clonidine may also make it physically possible to discharge patients from the PICU faster, but this adds an additional medication that will also need to be managed once the patient is discharged from the PICU. Having to taper this additional medication, in addition to weaning opioids and benzodiazepines and paring down a patient's medication regimen for discharge, could increase the potential for error. Yagiela et al⁹ reported that of 155 patients discharged after a PICU admission, 77% went home with a new medication. Even with a set plan and effective handover between the PICU and floor teams, there is potential increased risk for error either by prolonged therapy, miscommunication from practitioners, or poor patient compliance with a wean regimen.

We did not find that the addition of clonidine led to significant reductions in signs of withdrawal, with the exception of reducing postinfusion tachycardia. This postinfusion tachycardia was not shown to be clinically impactful, warranting any clinical interventions. Owing to the complexity of patients recovering from critical illness, these values could have also been reflective of other sequelae independent of the weaning of dexmedetomidine; and because the use of clonidine was

not done under a set protocol, but rather at the physician's discretion, it is possible that the rate of taper of clonidine could also have had an impact.

We also did not find that addition of clonidine increased the speed for weaning off the infusion or reduced the time to discharge from the PICU. We had hypothesized that patients who are transitioned to clonidine would have a quicker wean off dexmedetomidine than patients not initiated on clonidine. As our hospital does not allow dexmedetomidine infusions outside of the PICU, this could have led to sooner transfer out of the PICU and quicker discontinuation of central venous access. However, this hypothesis did not hold true in our study. In our study, patients in both groups were weaned off the dexmedetomidine infusion over 2 days and left the PICU the following day.

Previous studies have examined dexmedetomidine withdrawal. Whalen et al⁶ evaluated rates of withdrawal in children discontinuing dexmedetomidine by using the Withdrawal Assessment Tool (WAT-1). This verified tool is used to detect withdrawal from opioid and benzodiazepines by monitoring different symptoms of withdrawal including agitation, tremors, emesis, and decreased/increased sleep. It is important to note that this tool has not been validated in evaluating for withdrawal from dexmedetomidine. They showed that patients who had discontinued dexmedetomidine with a wean had a lower average withdrawal score at 24 and 48 hours than children who had discontinued without a wean. Lardieri et al,¹⁰ in a study that evaluated 19 patients, found children who received clonidine had a mean lower WAT-1 score (0.8; range, 0–6) than

Figure 2. Percentage of heart rate before and after discontinuation of dexmedetomidine.

Each dot represents a single patient's heart rate before and after discontinuation of dexmedetomidine. There was no statistically significant difference between baseline heart rates of each group ($p = 0.228$), or the baseline and post-discontinuation in the clonidine group ($p = 0.647$). There was a significant difference between the baseline and the post-discontinuation heart rate in the no clonidine group ($p = 0.008$).

children who did not receive clonidine (3.2; range, 0–8); however, this was not statistically significant ($p = 0.49$). They also found no difference in changes of the mean systolic blood pressures. However, there was a statistically significant increase in the heart rate before and after dexmedetomidine discontinuation between groups.¹⁰ Overall, our study found similar results to those of Lardieri et al,¹⁰ although we chose not to use WAT-1 scores because it is not a validated tool to assess for dexmedetomidine withdrawal and unfortunately, WAT-1 scores were not routinely being recorded at our institution during the time of this study.

Our investigation has several limitations based on the retrospective and pragmatic nature of the study. Most patients were also receiving opioids and/or benzodiazepines concurrently with dexmedetomidine, which is consistent with standard-of-care sedation in the PICU. Withdrawal symptoms from these medications can manifest similarly to withdrawal from dexmedetomidine, so it can be difficult to differentiate which medication is causing withdrawal. Although this is a potential concern, there was no difference in sedation management between the 2 groups, so opioid and/or benzodiazepine withdrawal being attributed to dexmedetomidine withdrawal or dexmedetomidine withdrawal being attributed to opioid and/or benzodiazepine would have the same potential for error in both groups.

Many patients in the PICU are receiving medications for heart rate and blood pressure control. Because the use of these medications could mask increases in heart rate and blood pressure associated with withdrawal from dexmedetomidine, we excluded patients receiving

medications for treatment of tachycardia and hypertension during the time of data collection. This could also have potentially excluded patients who did have severe withdrawal if these medications were started following dexmedetomidine discontinuation, creating a compounding variable. However, a similar percentage of patients were excluded for this indication in each group (35% in the clonidine and 30% in the no clonidine group [$p = 0.773$]), making this less of a concern.

Another limitation of our study is that the decision to add or not add clonidine, the dose of clonidine, and the approach to weaning dexmedetomidine were left up to the discretion of the clinical team and not dictated per protocol. Individual provider biases, based on anecdotal and past experiences, may have influenced these decisions, which could directly influence the likelihood of withdrawal and the duration of treatment and PICU admission. Terry et al¹¹ evaluated safety and efficacy of converting to enteral clonidine from dexmedetomidine infusions in adult patients. They found no differences in blood pressure and heart rate between the 2 groups. In our study, the median dose of clonidine was 4.5 mcg/kg/day, which is below what has been reported as being used by others.¹¹

Another challenge with a retrospective study is that it is dependent on accurate documentation. The vital signs we report are only stored in the EMR if the bedside nurse chooses to save them. Although they have orders to record vital signs in the patient orders (generally every 1 or 2 hours), they also have the ability to save other values at their own discretion. This creates the possibility for overreporting or underreporting vital sign

abnormalities. For agitation, our ability to accurately report recorded agitation is entirely dependent on nurses and physicians using language that was laid out in the study protocol. If alternative language was used, these occurrences of agitation would be missed. We also collected data on agitation only following dexmedetomidine discontinuation. This leaves potential for overestimating the rates of agitation if the patient was also agitated prior to dexmedetomidine discontinuation.

Lastly, we had a relatively small sample size. Our study population was recruited from 2015–2017. Prior to 2015, dexmedetomidine use was highly restricted at our institution owing to the high cost of the medication prior to the availability of the generic product. The small sample size limited our ability to perform a multivariate analysis examining variability in findings based on patient characteristics and treatment dosages. Additionally, the small sample size limited our ability to evaluate differences between patients receiving enteral clonidine and those who had a transdermal patch. An important next step in the evaluation of withdrawal prevention with prolonged dexmedetomidine use includes prospective studies evaluating a protocolized approach to preventing withdrawal.

Conclusions

With the increasing use of dexmedetomidine in PICUs, strategies need to be developed to assess for and prevent withdrawal. This retrospective study is one of the first to evaluate strategies for weaning dexmedetomidine infusions of >3 days. We did not report any major safety concerns with slowly weaning off a dexmedetomidine infusion without the addition of clonidine; however, this is a very small study and further prospective studies with clear protocols are necessary to better assess this potential strategy. Although this study is not able to definitively address all concerns with weaning of dexmedetomidine, we were able to show the addition of clonidine did not reduce the time to weaning off dexmedetomidine, or the length of PICU stay after the continuous infusion was completed.

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the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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 Exempt Approval by the appropriate committees at our institution (Protocol No. 1709369953).

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