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Incidence of Dexmedetomidine Withdrawal in Adult Critically Ill Patients: A Pilot Study

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Objectives: To determine the incidence of dexmedetomidine withdrawal in adult critically ill patients.

Design: This was a prospective, observational study of patients from November 2017 to December 2018.

Setting: Medical-surgical, cardiothoracic, and neurosurgical ICUs in a tertiary care hospital.

Patients: Adult critically ill patients on dexmedetomidine infusions for at least 3 days.

Interventions: Indicators of withdrawal were assessed at baseline and at least daily during the dexmedetomidine wean period. Delirium was assessed using the Confusion Assessment Method for the ICU.

Sedation was assessed using the Richmond Agitation-Sedation Scale. The Withdrawal Assessment Tool-1 was performed and vital signs were recorded during each assessment. Patients were considered positive for dexmedetomidine withdrawal if they had two or more of the following symptoms: positive Confusion Assessment Method for the ICU, Richmond Agitation-Sedation Scale greater than +1, positive Withdrawal Assessment Tool-1 assessment, tachycardia (heart rate > 90 beats/min), and hypertension (systolic blood pressure > 140 mm Hg or mean arterial pressure > 90).

Measurements and Main Results: Forty-two patients were included in the study, with 64% of patients experiencing signs of dexmedetomidine withdrawal. The median time on dexmedetomidine for all patients was 9.6 days (5.8–12.7 d), and the median dose of dexmedetomidine received was 0.8 µg/kg/hr (0.5–1 µg/kg/hr). Of the patients who were positive for withdrawal, the most prevalent withdrawal symptoms observed included delirium, hypertension, and agitation (93%, 48%, and 33%, respectively). We found no correlation between chronic opioid tolerance and incidence of withdrawal symptoms. Peak dexmedetomidine doses greater than 0.8 µg/kg/hr and cumulative daily doses of dexmedetomidine greater than 12.9 µg/kg/d were associated with a higher incidence of withdrawal.

Conclusions: The majority of patients in our study demonstrated signs that may be indicative of dexmedetomidine withdrawal. Peak and cumulative daily dexmedetomidine dose, rather than duration of therapy, may be associated with a higher incidence of withdrawal signs. Regular screening of patients on prolonged dexmedetomidine infusions is recommended to ensure safe and effective use in critically ill patients.

Key Words: critical care; critically ill; dexmedetomidine; intensive care unit; sedation; withdrawal

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Dexmedetomidine is an alpha2-adrenoceptor agonist that is Food and Drug Administration approved for short-term sedation in critically ill patients. Current manufacturer recommended usage of dexmedetomidine is not to exceed 24 hours (1). However, several studies have demonstrated safety and efficacy in dexmedetomidine use for up to 5 days (2–4).

Current guidelines endorse the use of dexmedetomidine to achieve light sedation in critically ill patients (5). Dexmedetomidine has a

rapid onset, relatively short duration of action, and minimal propensity to over-sedate patients. Additionally, it lacks respiratory depressant effects, which makes it a viable medication option for continuous sedation in both intubated and nonintubated critically ill patients. Due to its favorable sedative and anxiolytic profile, prolonged use of dexmedetomidine has become more common in many ICU settings.

In light of the widespread use of dexmedetomidine, case reports and retrospective studies of withdrawal after prolonged dexmedetomidine infusions have emerged in adult and pediatric patients. Reported withdrawal signs include hypertension, tachycardia, diaphoresis, anxiety, and altered mental status (6–14). The timeframe in which withdrawal can be expected is currently unknown. Furthermore, information regarding risk factors for dexmedetomidine withdrawal are currently limited.

The objective of this study was to evaluate the incidence of dexmedetomidine withdrawal in adult critically ill patients and to characterize the risk factors associated with an increased risk of withdrawal.

MATERIALS AND METHODS

This was a prospective, observational study conducted at a single large academic medical center. Institutional Review Board approval was obtained prior to subject enrollment. Formal informed consent was waived given regular withdrawal monitoring by ICU pharmacists at our institution. Adult patients in the medical-surgical, cardiothoracic and neurosurgical ICUs receiving dexmedetomidine for greater than 3 days without interruption of infusion for greater than 6 hours were evaluated for inclusion into the study. The evaluation period began when weaning of dexmedetomidine was initiated and ended 48 hours after the drug was discontinued. Chemically paralyzed, incarcerated, or pregnant patients were excluded from this study.

Initial screening for patients was performed using the electronic medical record system. Subsequently, study investigators performed in-person assessments for signs of withdrawal in included subjects at least one time per day throughout the evaluation period. The evaluation period began upon a decrease in dexmedetomidine infusion from the peak rate (or when the decision to wean was noted by the prescribing team) and ended 48 hours after the drug was discontinued. Assessments included evaluation of blood pressure, heart rate, Richmond Agitation-Sedation Scale (RASS) (15–18), and Confusion Assessment Method for the ICU (CAM-ICU) (19, 20). Given recent data using the Withdrawal Assessment Tool (WAT)–1 in pediatric patients experiencing dexmedetomidine withdrawal, we also performed the WAT-1 during each assessment and evaluated each component of the tool individually (20, 21).

Patients were considered positive for withdrawal if they had at least two signs of withdrawal during a single assessment. Signs of withdrawal were characterized by the following: tachycardia defined as a heart rate greater than 90 beats per minute, hypertension defined as a systolic blood pressure greater than 140 mm Hg or mean arterial pressure greater than 90, RASS greater than +1, positive CAM-ICU, and a WAT-1 score greater than or equal to 3. Additional information collected included basic demographic information such as age, sex, reason for ICU admission, ICU length of stay, and hospital length of stay. The presence of chronic opioid tolerance was defined as opioid use equal to or greater than 60 milligrams of morphine

equivalents for greater than 7 days prior to study enrollment (i.e., beginning of dexmedetomidine wean). Identification of patients with concurrent use of other sedative and analgesic medications was performed in an effort to control for potential confounders. Clonidine taper use was allowed and recorded per provider discretion to wean off of prolonged dexmedetomidine infusion. The clonidine taper algorithm and dosing administered was based on a previous pilot study by Gagnon et al (22).

Standard t tests or Mann-Whitney U tests were used to compare continuous variables; chi-square or Fisher exact tests were used to compare nominal variables. To examine the association between two or more withdrawal symptoms and dexmedetomidine exposure (cumulative dose, peak rate, and time on dexmedetomidine), a multivariate regression analysis was performed to control for potential confounders, including concurrent sedative use and opioid tolerance at time of assessment. Receiver operating characteristic (ROC) curves and Youden's statistical analysis were used to evaluate the sensitivity and specificity of cumulative daily dexmedetomidine dose and peak dexmedetomidine dose with the incidence of two or more withdrawal symptoms. Data were analyzed using STATA software Version 14 (StataCorp LP, College Station, TX).

RESULTS

There were 780 ICU patients screened (**Fig. 1**) for the presence of prolonged dexmedetomidine use (i.e., > 3 d). Forty-two patients were included in the study, with 27 (64%) patients experiencing signs and symptoms consistent with dexmedetomidine withdrawal. Patient characteristics are noted in **Table 1**. There were no differences between groups in terms of baseline demographic data, reason for ICU admission, ICU length of stay, concurrent sedative use, or opioid tolerance at the time of assessment. The majority of patients in the study were in the medical-surgical ICU.
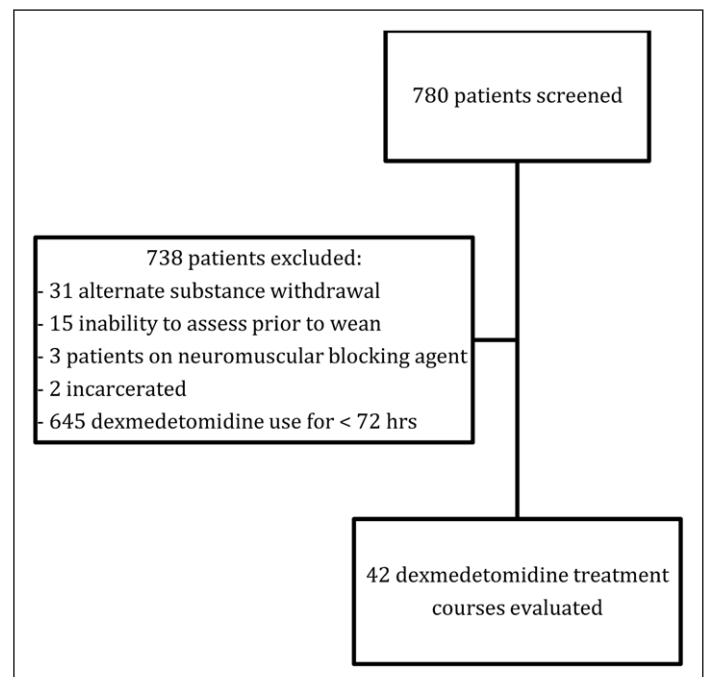

Figure 1. Patients screened and included.

TABLE 1. Patient Characteristics

Characteristics	Negative Withdrawal (< 2 Withdrawal Symptoms) (n = 15)	Positive Withdrawal (≥ 2 Withdrawal Symptoms) (n = 27)	p
Age, yr, median (IQR)	59 (51–74)	54 (45–65)	0.64
Male sex, n (%)	8 (53)	19 (70)	0.29
Sequential Organ Failure Assessment score, median (IQR)	10 (8–11)	10 (9–14)	0.24
Type of ICU, n (%)			
Medical/surgical	8 (53)	15 (56)	1
Cardiovascular	4 (27)	7 (26)	0.72
Neurologic	3 (20)	5 (19)	1
ICU length of stay, d, median (IQR)	16.5 (13.5–32.3)	19.5 (14.6–35)	0.54
Failed dexmedetomidine wean, n (%)	5 (33)	12 (44)	0.53
Sedative administration at time of assessment, n (%)	4 (27)	9 (33)	0.74
Opioid tolerance at time of assessment, n (%)	8 (53)	16 (59)	0.75

IQR = interquartile range.

The median number of assessments conducted per patient was 3 (2–3). The most common withdrawal symptoms experienced included delirium, hypertension, and anxiety (**Table 2**). Dexmedetomidine characteristics of patients who experienced withdrawal compared with those who did not can be found in **Table 3**. The median time on dexmedetomidine for all patients before enrollment into the study was approximately 8 days (4.3–10 d). There was a statistically significant difference in median dexmedetomidine peak rate between patients who experienced withdrawal compared with those who did not (1 µg/kg/hr [0.8–1.2 µg/kg/hr] vs 0.7 µg/kg/hr [0.5–1 µg/kg/hr], respectively; p = 0.02). The number of days on dexmedetomidine was not associated with a higher incidence of withdrawal. Nor were the cumulative dexmedetomidine dose received per day or dose for all days combined significantly different between groups. Clonidine was used in 37% of patients that displayed signs of potential dexmedetomidine withdrawal; however, the use of clonidine was not associated with a difference in withdrawal symptoms.

ROC curves are displayed in **Figure 2**. A cumulative dexmedetomidine dose greater than 12.9 µg/kg/d was associated with withdrawal with an 85.2% sensitivity and 53.3% specificity (area under the curve [AUC], 0.72; 95% CI, 0.55–0.88). Doses greater than 0.8 µg/kg/hr were associated with withdrawal with a 77.8% sensitivity and 60% specificity (AUC, 0.71; 95% CI, 0.53–0.88). Using the findings of the ROC curves, patients receiving a peak rate greater than 0.8 µg/kg/hr and a cumulative dose greater than 12.9 µg/kg/d were examined between the two groups. Dexmedetomidine peak rate greater than 0.8 µg/kg/hr was associated with a significantly higher incidence of withdrawal (33% vs 78%; p = 0.01) (Table 3). In addition, cumulative dexmedetomidine doses greater than 12.9 µg/kg/d were also associated with higher incidence of withdrawal (47% vs 81%; p = 0.04).

Two multivariate regression analyses were performed (cumulative dexmedetomidine dose received per day and peak dexmedetomidine rate) to control for concurrent sedative use and opioid tolerance at time of assessment. The cutoffs for cumulative dexmedetomidine dose received per day and peak dexmedetomidine rate were derived from the results of the ROC curves (> 12.9 µg/kg/d and 0.8 µg/kg/hr, respectively). When controlling for concurrent sedative use and opioid tolerance, cumulative dexmedetomidine dose greater than 12.9 µg/kg/d remained significantly associated with greater odds of withdrawal when compared with lower doses (odds ratio [OR], 4.94 [1.2–20.3]; p = 0.03). In addition, peak dexmedetomidine rates greater than 0.8 µg/kg/hr remained significantly associated with greater odds of withdrawal when compared with lower peak rates (OR, 8 [1.8–35.7]; p < 0.01).

DISCUSSION

Dexmedetomidine use in the ICU has become significantly more common in light of updated clinical practice guidelines for ICU sedation (5). Dexmedetomidine is one of the preferred agents of use for sedation in the ICU due to its light sedative properties, a lower incidence of associated delirium, and decreased time on the ventilator when compared with other agents such as benzodiazepines and propofol (2–4). Dexmedetomidine also has the advantage in flexibility of use as a sedative in both intubated and nonintubated patients.

With increased use, however, reports have emerged of withdrawal symptoms after prolonged infusions of dexmedetomidine in both adult and pediatric patients (6–14). The most common withdrawal symptoms previously reported include hypertension, tachycardia, diaphoresis, agitation, and altered mental status (6–14). In a case report by Kukoyi et al (14), adult patients experienced acute agitation, hypertension, and tachycardia with the abrupt discontinuation of dexmedetomidine. In a recent study of pediatric patients by Haenecour et al (12), the most common symptoms of withdrawal were agitation, fever, loose stools, and insomnia. In our study population, we similarly found the most common symptoms during dexmedetomidine wean to be delirium, hypertension, and agitation, consistent with previous studies and case reports in adult and

TABLE 2. Withdrawal Symptoms Observed

Symptoms Experienced	Negative Withdrawal (n = 15)	Positive Withdrawal (n = 27)	p
Individual withdrawal symptoms, n (%)			
RASS > +1	0	9 (33)	0.02
Confusion Assessment Method ICU +	3 (20)	25 (93)	< 0.01
Systolic blood pressure > 140 mm Hg or mean arterial pressure > 90 mm Hg	1 (7)	13 (48)	0.01
Heart rate > 90 beats/min	9 (60)	23 (85)	0.13
WAT-1 ≥ 3	0	3 (11)	0.54
Individual WAT-1 components			
Pre-stimulus			
Loose/watery stools	6 (40)	10 (37)	1
Vomiting	0	3 (11)	0.54
Temperature > 37.8°C	2 (13)	9 (33)	0.27
RASS > 0	0	10 (37)	< 0.01
Moderate-severe tremor	0	0	1
Diaphoresis	0	4 (15)	0.28
Yawning or sneezing	0	0	1
Moderate-severe repetitive movements	0	1 (4)	1
Post-stimulus			
Moderate-severe startle to touch	0	0	1
Increased muscle tone	0	0	1
2+ min to return to calm state	0	0	1
5+ min to return to calm state	0	0	1

RASS = Richmond Agitation-Sedation Scale, WAT-1 = Withdrawal Assessment Tool-1.

TABLE 3. Dexmedetomidine Characteristics

Characteristics	Negative Withdrawal (< 2 Symptoms) (n = 15)	Positive Withdrawal (≥ 2 Symptoms) (n = 27)	p
Total time on dexmedetomidine (d) prior to wean (d), median (IQR)	8.3 (3.7–11)	7.5 (4.7–9.8)	0.96
Dexmedetomidine peak rate (μg/kg/hr), median (IQR)	0.7 (0.5–1)	1 (0.8–1.2)	0.02
Total time on dexmedetomidine (d), median (IQR)	10.4 (5–13.5)	9.5 (6.1–12.5)	0.74
Cumulative dexmedetomidine dose received per day (μg/kg/d), median (IQR)	12.8 (11.1–18.6)	20.4 (14.5–25.8)	0.11
Total cumulative dexmedetomidine dose received (μg/kg), median (IQR)	138 (64.4–214.8)	176.3 (109–289)	0.24
Dexmedetomidine peak rate > 0.8 μg/kg/hr, n (%)	5 (33)	21 (78)	< 0.01
Cumulative dexmedetomidine dose received per day > 12.9 μg/kg/d, n (%)	7 (47)	22 (81)	0.04

IQR = interquartile range.

pediatric critically ill patients (6–14). This is the first study to directly observe the incidence of withdrawal experienced during weaning after prolonged dexmedetomidine use in adult ICU patients.

Haenecour et al (12) evaluated the association between withdrawal symptoms and cumulative dexmedetomidine exposure in pediatric patients and found that dexmedetomidine cumulative doses of 107 μg/kg prior to initiation of wean was more likely to be associated with withdrawal. In our study, we found the total cumulative dose of dexmedetomidine was not found to be significant for withdrawal symptoms. Instead, cumulative daily dexmedetomidine doses of greater than 12.9 μg/kg/d and peak dexmedetomidine rates greater than 0.8 μg/kg/hr were associated with withdrawal. The differences in findings
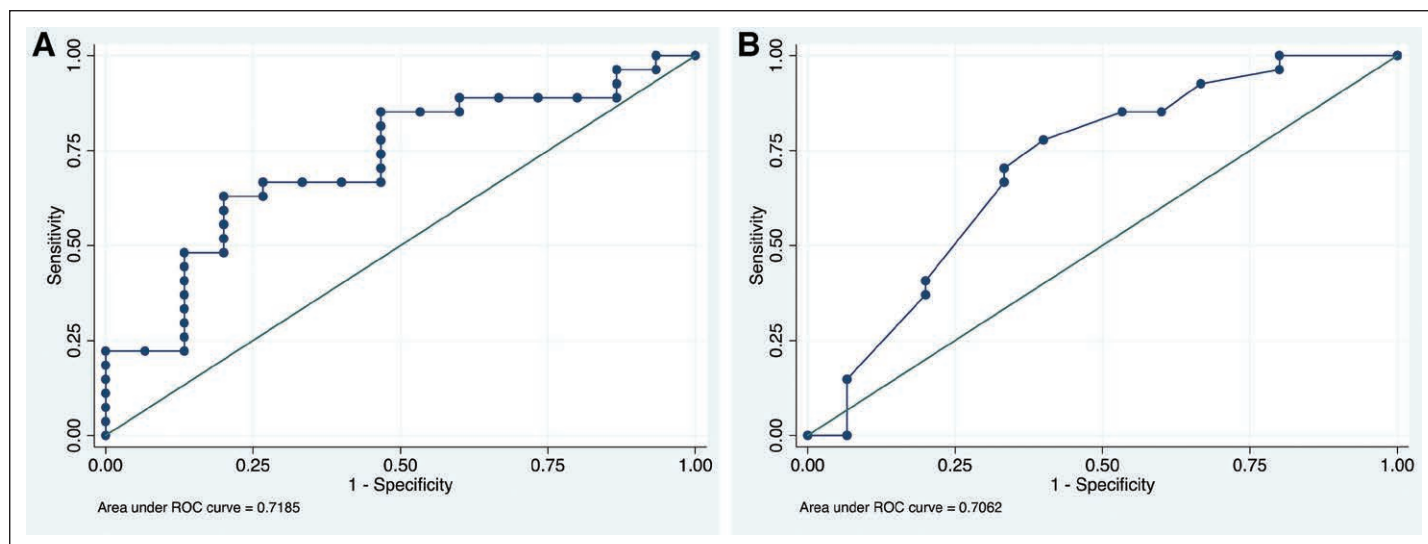
Figure 2. Receiver operating characteristic (ROC) curves. **A**, Cumulative dexmedetomidine dose (μg/kg/d). Area under the curve (AUC), 0.72; 95% CI, 0.55−0.88, dexmedetomidine withdrawal was associated with a cumulative dexmedetomidine dose 12.9 μg/kg/d (85.2% sensitivity and 53.3% specificity). **B**, Maximum dexmedetomidine rate (μg/kg/hr). AUC, 0.71; 95% CI, 0.53−0.88, dexmedetomidine withdrawal was associated with a maximum dexmedetomidine rate of 0.8 μg/kg/hr (77.8% sensitivity and 60% specificity).

could be attributed to the large number of patients in our study that were on lower dexmedetomidine doses for prolonged periods of time without apparent withdrawal symptoms. Alternately, higher doses of dexmedetomidine for prolonged periods of time were associated with higher risk for withdrawal symptoms in our patients.

In a recent study surveying withdrawal concerns in the PICU, 87.8% of intensive care physicians had concerns regarding dexmedetomidine withdrawal and 45.7% expressed concerns with longer duration of infusion (over 120 hr) (23). Our study suggests that screening for risk for withdrawal should be done based on peak dose and cumulative daily exposure to dexmedetomidine. Duration of dexmedetomidine use at lower doses does not appear to be associated with higher risk for withdrawal symptoms. Due to frequent titration of dexmedetomidine infusions, we were unable to accurately assess the optimal wean strategy or duration of dexmedetomidine wean after prolonged infusion. More studies evaluating weaning techniques and withdrawal assessments may be helpful to evaluate the optimal strategy for dexmedetomidine discontinuation after prolonged infusion. However, the findings of this study suggest that patients receiving high infusion rates should be monitored more closely for withdrawal.

Multiple published studies suggest the safety and efficacy of dexmedetomidine transition to clonidine for sedation (22,24–26), and clonidine was used in 37% of patients that displayed signs of potential dexmedetomidine withdrawal. The use of clonidine in our study was not associated with a difference in withdrawal symptoms. However, given that clonidine does not require ICU titration, is significantly more cost-effective, and requires less frequent monitoring, the use of clonidine may be a viable option to transition patients off of prolonged dexmedetomidine infusions.

There are several limitations to this study. This was a single-center study with a relatively small sample size. However, given the anticipated effect size and prospective nature of our study, this sample should be sufficient to evaluate the proposed outcome. Another limitation was that approximately one-third of patients in this study received clonidine due to concern for withdrawal after weaning dexmedetomidine. The use of clonidine may have masked some of the symptoms of withdrawal seen in these patients, and further studies are needed to evaluate the impact of clonidine on withdrawal symptoms in adult patients. In addition, there is no validated WAT in adults at this time, so a modified assessment tool based on the literature available in pediatric and adult patients was created for use in this study. Given these findings, a WAT may be beneficial in identifying withdrawal among critically ill patients on dexmedetomidine. Lastly, the majority of patients in this study were from the medical-surgical ICU population, and larger studies in various subpopulations would be needed to extrapolate findings to more critically ill patients.

CONCLUSIONS

Our study demonstrated that dexmedetomidine withdrawal is prevalent among critically ill patients receiving prolonged infusions. Withdrawal may be more likely to occur in patients receiving high cumulative daily doses or high peak rates of dexmedetomidine (> 12.9 μg/kg/d or > 0.8 μg/kg/hr) for more than 3 days. Future studies are needed to validate these findings, in addition to examining the utility of a standardized weaning algorithm for patients on dexmedetomidine infusions.

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