

Dexmedetomidine and Iatrogenic Withdrawal Syndrome in Critically Ill Children

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BACKGROUND Iatrogenic withdrawal syndrome is a well-known adverse effect of sedatives and analgesics commonly used in patients receiving mechanical ventilation in the pediatric intensive care unit, with an incidence of up to 64.6%. When standard sedative and analgesic treatment is inadequate, dexmedetomidine may be added. The effect of supplemental dexmedetomidine on iatrogenic withdrawal syndrome is unclear.

OBJECTIVE To explore the potentially preventive effect of dexmedetomidine, used as a supplement to standard morphine and midazolam regimens, on the development of iatrogenic withdrawal syndrome in patients receiving mechanical ventilation in the pediatric intensive care unit.

METHODS This retrospective observational study used data from patients on a 10-bed general pediatric intensive care unit. Iatrogenic withdrawal syndrome was measured using the Sophia Observation withdrawal Symptoms-scale.

RESULTS In a sample of 102 patients, the cumulative dose of dexmedetomidine had no preventive effect on the development of iatrogenic withdrawal syndrome ($P = .19$). After correction for the imbalance in the baseline characteristics between patients who did and did not receive dexmedetomidine, the cumulative dose of midazolam was found to be a significant risk factor for iatrogenic withdrawal syndrome ($P < .03$).

CONCLUSION In this study, supplemental dexmedetomidine had no preventive effect on iatrogenic withdrawal syndrome in patients receiving sedative treatment in the pediatric intensive care unit. The cumulative dose of midazolam was a significant risk factor for iatrogenic withdrawal syndrome. (*Critical Care Nurse*. 2021;41[1]:e17-e23)

Sedative and analgesic treatment with benzodiazepines and opioids is often needed in critically ill patients receiving mechanical ventilation in the pediatric intensive care unit (PICU).^{1,2} A potential complication of this sedative and analgesic treatment is iatrogenic withdrawal syndrome (IWS). This syndrome is a serious condition that may occur when an analgesic or sedative drug is too abruptly decreased or stopped.^{3,4} Symptoms include tachycardia, pyrexia, discomfort, anxiety, muscle tension, disturbed sleeping pattern, diarrhea, and vomiting.⁵⁻⁷ The reported incidence of IWS in sedated PICU

patients varies significantly but is as high as 64.6%,^{3,5,8-11} with the cumulative doses and duration of sedative and analgesic drug treatment, presence of cognitive impairment, and young age being the most important risk factors.^{3,5,12-15} Iatrogenic withdrawal syndrome can be prevented and treated by more gradual weaning of sedatives and analgesics with oral equivalents.¹⁶⁻¹⁸ Although this process can be safely carried out even outside a PICU setting, the patient must remain in the hospital; therefore, more gradual weaning regimens or treatment of IWS can result in longer intensive care unit and hospital stays.¹⁹⁻²¹

Finding the optimal level of sedation can be challenging, and signs of patient discomfort may be present despite appropriate use of the conventionally used sedatives and analgesics such as midazolam and morphine. Dexmedetomidine has recently been introduced as a supplemental agent with the aim of optimizing sedation levels without increasing the doses of currently used sedatives and

analgesics.^{22,23}

It has been theorized that dexmedetomidine use might prevent the development of IWS

associated with benzodiazepines and opioids.²⁴ Dexmedetomidine is an α_2 -agonist and has both sedative and analgesic effects. It was approved by the US Food and Drug Administration in 1999 for short-term sedation in adults in an intensive care setting.²⁵ The safety and efficacy of dexmedetomidine in children remain

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unclear²⁶⁻³² and to date have been evaluated only in small trials.^{22,25-30,32-36} When used in addition to morphine and midazolam to achieve a more optimal level of sedation, dexmedetomidine might reduce the incidence of IWS in children, but the results of the trials evaluating the preventive effect of dexmedetomidine on IWS are contradictory. Therefore, the aim of this study was to explore the possible preventive effect of dexmedetomidine, when used in addition to morphine and midazolam, on the development of IWS in patients receiving mechanical ventilation in the PICU.

Methods

Setting and Study Population

We conducted this study in a tertiary PICU in a single university hospital. This general PICU has 10 beds and provides care for approximately 550 intensive care patients annually, ranging in age from newborn to 18 years.

The study included all patients admitted to the PICU between January 1, 2016, and December 6, 2018, who underwent mechanical ventilation and received sedative treatment with morphine and midazolam for at least 48 hours continuously. Midazolam and morphine were administered and dose adjustments were made according to a sedation and analgesic protocol, which was part of standard patient care. Midazolam and morphine were started on a low continuous dosage and, when necessary, increased to a maximum continuous dosage of 0.3 mg/kg/h midazolam and 30 μ g/kg/h morphine. If sedation levels remained unsatisfactory, dexmedetomidine was started as an adjuvant treatment. The continuous dosage of dexmedetomidine was adjusted to reach the optimal level of sedation, to a maximum dosage of 1.5 μ g/kg/h. No loading dose was administered when dexmedetomidine was started. Sedation levels were assessed using the COMFORT behavioral scale. When the patient was deemed ready for extubation, analgesic and sedative treatment was gradually weaned and stopped following a protocol that specifies a decrease in continuous dosage of midazolam of 0.05 mg/kg/h every 8 hours and a decrease of morphine of 5 μ g/kg/h every 8 hours. The dexmedetomidine dose was decreased by 0.2 μ g/kg/h every 8 hours.

Patients transferred to another PICU during sedative treatment, those who died during sedative treatment, and those who received clonidine were excluded from the study. Patients who received clonidine were excluded to avoid bias. Both clonidine and dexmedetomidine are

α_2 -agonists and have similar mechanisms of action. In addition, clonidine is used to treat acute withdrawal syndrome in adults.²⁵

Design and End Points

The primary outcome of this retrospective observational study was the incidence of IWS, measured using the Sophia Observation withdrawal Symptoms-scale (SOS), after administration of continuous sedative and analgesic treatment for a minimum of 48 hours.^{10,11,36,37} The SOS assesses 15 clinical items, each of which is given a score of 0 or 1 point, resulting in a maximum score of 15.¹¹ The validity of the SOS was evaluated in a prospective study in which it was compared with the Numeric Rating Scale Withdrawal tool, another withdrawal scoring instrument.¹¹ The results of that study showed acceptable sensitivity and specificity of 83% and 93%, respectively.^{11,37} The patient's level of sedation and distress was measured with the COMFORT behavioral scale.³⁸ This scale assesses 6 behavioral items, each of which has 5 response alternatives rated from 1 to 5, resulting in a total score of between 6 and 30.³⁹ A score between 11 and 17 was considered to indicate an optimal level of sedation. In a systematic review, the clinimetric properties of this scale were assessed.³⁸ Most studies showed internal consistency and interrater reliability values of greater than 0.70, indicating adequate reliability.³⁸

Data Collection

To evaluate the preventive effect of supplemental dexmedetomidine on the development of IWS, we recorded the following data: exposure to dexmedetomidine, median dosage ($\mu\text{g}/\text{kg}/\text{h}$), cumulative dose ($\mu\text{g}/\text{kg}$), and total duration of dexmedetomidine administration (hours), including the duration of weaning (hours). In addition, the following risk factors were assessed: age, risk of death, presence of cognitive impairment, duration of mechanical ventilation, length of PICU stay, total duration of morphine treatment, cumulative and average doses of morphine ($\mu\text{g}/\text{kg}$), total duration of midazolam treatment, cumulative and average doses of midazolam (mg/kg), and total duration of sedative administration.^{5,6,13,37,40} All available data were collected from the electronic health record (EHR) system and entered directly into a research database.

The SOS and the COMFORT scale are used in standard nursing care, and the resulting scores are recorded

in the EHR for all patients who are sedated for at least 72 hours. Both scores are assessed at least 3 times a day, with more frequent assessment when the patient shows signs of IWS or discomfort. The cumulative dose of medication was calculated by multiplying the dosage by the duration of treatment. The dosage and duration of medication are ordered by a physician and then recorded in the EHR by a nurse. Duration of mechanical ventilation, length of PICU stay, primary diagnosis, and Pediatric Risk of Mortality (PRISM III) score were collected in a separate database. The research database programs used were Microsoft Excel and Microsoft Access, and the data were combined into a single Excel database upon completion of data collection. Data collection was performed by 2 of the authors (B.M.G. and C.S.W.).

Statistical Analysis

For continuous variables with a normal distribution, the mean and SD are presented; otherwise, the median and interquartile range (IQR) are presented. For dichotomous variables, frequencies and percentages were calculated. Univariate analysis was used to compare patients with and without dexmedetomidine exposure. Statistical uncertainty

was expressed using the 95% CI, and $P \leq .05$ was considered statistically significant. Variables for which a statistically significant difference was found between patients who did and did not receive dexmedetomidine were included in a multivariate model.

To correct for any significant differences between the groups with and without dexmedetomidine exposure that could result in confounding by indication, we calculated a propensity score for baseline characteristics and included the propensity score in the multivariate analysis. All data were analyzed using the software package R Statistics version 1.0.153 for Mac.

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Results

Characteristics of the Sample

A total of 167 patients were eligible for inclusion in the study. Of these, 25 patients were transferred to another PICU during treatment, 24 patients died, and 16 received clonidine, resulting in a sample of 102 patients included

Table 1 Characteristics of patients

Characteristic	Total (N=102)	Patients given dexmedetomidine (n=56)	Patients not given dexmedetomidine (n=46)	P
Age, median (IQR), mo	6.5 (2-35)	14 (3-65)	2 (1-7)	<.001
Sex, No. (%)				
Male	57 (55.9)	33 (58.9)	24 (52.2)	.55
Female	45 (44.1)	23 (41.1)	22 (47.8)	
Weight, median (IQR), kg	7.3 (3.9-13.0)	10.3 (6.0-18.3)	4.7 (3.4-7.5)	<.001
Length, median (IQR), cm	77.6 (54.0-88.0)	80.0 (62.0-102.0)	57 (52.0-62.0)	<.001
PRISM III score, median (IQR)	4 (2-8)	3 (2-8)	5 (3-7)	.058
Primary diagnosis, No. (%)				
Respiratory	83 (81.4)	44 (78.6)	39 (84.8)	.64
Circulatory	2 (2.0)	1 (1.8)	1 (2.2)	
Trauma	3 (2.9)	2 (3.6)	1 (2.2)	
Postoperative	9 (8.8)	7 (12.5)	2 (4.3)	
Other	5 (4.9)	2 (3.6)	3 (6.5)	
Cognitive impairment, No. (%)				
Yes	13 (12.7)	7 (12.5)	6 (13.0)	> .99
No	89 (87.3)	49 (87.5)	40 (87.0)	
Comorbidity, No. (%)				
Yes	47 (46.1)	28 (50.0)	19 (41.3)	.43
No	55 (53.9)	28 (50.0)	27 (58.7)	
Duration of mechanical ventilation, median (IQR), d	6.0 (4.0-8.0)	5.0 (4.0-8.0)	6.0 (4.8-9.0)	.25
Length of stay in PICU, median (IQR), d	8.0 (6.0-11.0)	7.0 (6.0-11.5)	8.0 (6.0-10.8)	.85
COMFORT scale score, median (IQR)				
Median	13 (12-14)	13 (12-15)	12 (11-13)	.02
Minimum	8 (7-9)	9 (7-9)	8 (7-9)	.46
Maximum	20 (16-24)	21 (17-24)	20 (16-23)	.22
SOS score, median (IQR)				
Median	2 (1-3)	2 (1-3)	3 (1-4)	.51
Minimum	0 (0-1)	0 (0-0)	0 (0-1)	.57
Maximum	6 (3-8)	5 (3-7)	7 (3-8)	.34

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit; PRISM III, Pediatric Risk of Mortality; SOS, Sophia Observation withdrawal Symptoms-scale.

in the final analysis. The median age was 6.5 (IQR, 2-35) months, 57 patients (55.9%) were male, and the median duration of mechanical ventilation was 6 (IQR, 4-8) days (Table 1). In total, 63 (61.2%) patients developed IWS.

Univariate Analysis

Of the 102 patients, 56 (54.9%) received supplementary dexmedetomidine. Statistically significant differences were found in patient age, weight, length, and median COMFORT scale score between the group that received dexmedetomidine and the group that did not (Table 1).

Propensity Score

The significant differences found in univariate analysis indicated confounding by indication. Therefore, baseline characteristics (age, sex, weight, length, PRISM III score, primary diagnosis, presence of comorbidity,

presence of cognitive impairment, minimum COMFORT scale score, maximum COMFORT scale score, and median COMFORT scale score) were summarized into a propensity score. The median propensity score for patients who were treated with dexmedetomidine was higher (0.82) than that for patients who were not treated with dexmedetomidine (0.37). This finding indicates that, on the basis of baseline characteristics, patients exposed to dexmedetomidine had a higher chance of being exposed to dexmedetomidine than patients who were not exposed to dexmedetomidine.

Multivariate Analysis

When the cumulative doses of dexmedetomidine, morphine, and midazolam and the propensity score were combined in a multivariate model, the cumulative dose of dexmedetomidine had no preventive effect on

Table 2 Logistic regression analysis

	Regression coefficient (SE)	Odds ratio (95% CI)	P
Intercept	-1.38 (0.68)	0.25 (0.06-0.91)	.04
Morphine cumulative dose, µg/kg	0.0004 (0.00027)	1.00 (1.00-1.00)	.09
Midazolam cumulative dose, mg/kg	0.089 (0.03)	1.09 (1.04-1.17)	.003
Dexmedetomidine cumulative dose, µg/kg	0.0059 (0.004)	1.01 (1.00-1.02)	.19
Propensity score	-0.511 (0.9)	0.60 (0.10-3.42)	.57

the subsequent development of IWS ($P=.19$). Furthermore, we found that only the cumulative dose of midazolam was a significant risk factor for development of IWS (odds ratio, 1.09 [95% CI, 1.04-1.17]; $P<.03$), whereas the cumulative dose of morphine was not (odds ratio, 1.00 [95% CI, 1.00-1.00]; $P=.09$). Further details are shown in Table 2.

Discussion

In this study, we aimed to explore the possible preventive effect of supplementary dexmedetomidine on the development of IWS in critically ill children undergoing mechanical ventilation who received continuous intravenous midazolam and morphine. We found that dexmedetomidine had no preventive effect on the development of IWS in our cohort.

Although the cumulative dose of dexmedetomidine had no preventive effect, it did not appear to be a risk factor for the development of IWS. These findings are similar to the results of previous studies.^{25,26} However, some controversy remains, as Haenecour et al³⁰ found that the cumulative dose of dexmedetomidine was a significant risk factor for IWS. More recently, in a study in which dexmedetomidine was used as a single continuous sedative agent during noninvasive ventilation, Shutes et al⁴¹ found that patients with a higher cumulative dose of dexmedetomidine had an increased risk of IWS. However, taking into account both our results and the findings from previous research, it is difficult to draw firm conclusions regarding the potential risk or benefit posed by dexmedetomidine in the development of IWS. Also, the fact that we used dexmedetomidine as a supplement to standard sedative and analgesic treatment with benzodiazepines and opioids, which are themselves independent risk factors for IWS development,^{22,28-30,32,42,43} influences the conclusions that are drawn. Perhaps the greatest challenge is to distinguish the individual agent responsible for causing IWS in each patient.

Before beginning our study, we assumed that the addition of supplementary dexmedetomidine in cases of unsatisfactory sedation levels would allow achievement of an optimal level of sedation without the need for increased doses of other sedatives, which might prevent or decrease the risk of IWS. Contrary to our hypothesis, however, we found that median continuous dosages of morphine and midazolam were even higher in patients receiving dexmedetomidine, although this difference was not significant. Dexmedetomidine is used as an adjuvant more frequently in patients in whom optimal levels of sedation have not been reached, and the patients in

this study who were treated with dexmedetomidine had significantly higher median COMFORT scale scores, as shown in Table 1. This situation could account for the higher median continuous dosages of midazolam and morphine recorded for this patient group. The cumulative dose of midazolam is an independent risk factor for the development of IWS, which might explain the lack of a preventive effect of dexmedetomidine on the development of IWS in our cohort. The results might be different when dexmedetomidine is prescribed as a primary sedative agent.

In accordance with previous research, we found that the cumulative dose of midazolam was a significant risk factor for development of IWS.^{3,5,8,9,11,12-14,43} In previous research with larger cohorts, multivariate analysis revealed more statistically significant predictors: duration of midazolam administration, duration of morphine administration, the number of additional sedatives/opioids, the length of analgesic therapy, commencement of gradual tapering, a younger age, mean daily opioid dose, and preexisting cognitive impairment.^{3,5,11,12-14} In research with a similar cohort

A nurse-driven pediatric sedation protocol can reduce withdrawal symptoms in patients admitted to the PICU.

size, only the peak and cumulative doses of midazolam remained statistically significant.^{8,9,14}

Incidence of IWS

We found a high incidence of IWS in our cohort (61.2%), although this finding was similar to the rate reported in previous studies (up to 64.6%).^{5,8-11} A possible explanation for the high incidence in our study is that in our study population the diagnosis of IWS was made when a single score of the SOS was 4 or higher. It could be argued that using only 1 score without confirmation might result in false classification and an overestimation of the incidence of IWS. However, on the basis of the clinimetric performance of the SOS in a prospective study evaluating its validity,¹¹ we believe that the relatively high incidence found in our cohort is likely correct.

Recommendations for Nursing Practice

Assessment of patients' level of comfort and sedation and, when necessary, making adjustments to sedative and analgesic treatment are part of specialist nursing care in the intensive care unit. A nurse-driven pediatric sedation protocol can reduce withdrawal symptoms in patients admitted to the PICU,^{44,45} and a sedative and analgesic drug rotation protocol can also help to reduce the risk of IWS.⁴⁶ Therefore, nurses must fully understand the clinical consequences and potential side effects of sedative and analgesic therapy and the potential risk factors for development of IWS. A better understanding of sedation weaning protocols and risk stratification for IWS can be helpful to nurses in assessing and reducing the risk of IWS in patients admitted to the PICU.⁴⁴

Future Research

Dexmedetomidine is currently approved only for use in adults in an intensive care setting.²⁵ All pediatric use at this time remains off-label. To ensure that children are treated with medications that are fully tested in their population, more prospective research is needed to determine the most appropriate treatment and dosing regimen of dexmedetomidine in critically ill children. In particular, a randomized controlled trial targeting dose finding and efficacy of dexmedetomidine in children is urgently needed. Finally, given the increased risk of IWS posed by midazolam use, more prospective studies are needed to determine the

suitability of dexmedetomidine as an effective primary sedative drug and an alternative to midazolam.

Limitations

Our study has some limitations. Importantly, all data were gathered retrospectively after reviews of the patient records. Data collected in this way must always be interpreted with caution. The results of this type of retrospective research are dependent on the accuracy of the information documented by physicians and nurses. This type of study carries a risk of incomplete data, although we found no obviously missing data in the medication records. Second, we used the SOS to diagnose IWS in children who were treated for a minimum of 48 hours, whereas the SOS has been validated only for treatment of at least 72 hours.^{7,11,37}

Third, owing to overlap in symptoms, distinguishing a patient with IWS from one with delirium is difficult in daily practice.⁴⁷ Recent research has combined the assessment of IWS with that of delirium in the SOS-Pediatric Delirium, suitable for use in children older than 3 months.⁴⁸ However, this screening tool was not in use at the time of this study, and therefore it is uncertain whether the children diagnosed with IWS actually had IWS or delirium. Finally, this research was performed at a single-center PICU, and generalizability of the results to a wider population may be limited.

Conclusion

The results of this study indicate that use of dexmedetomidine as a supplement to the conventionally used sedative drug regimen in the PICU has no preventive effect on the development of IWS. These results should be confirmed in future prospective studies. Dexmedetomidine may have a prominent place in the sedative regimens of critically ill children, but it should be used with caution. Although our results do not allow us to draw firm conclusions about the preventive effect of dexmedetomidine on the development of IWS, they do indicate that the cumulative dose of midazolam is a significant independent risk factor for the development of IWS. **CCN**

Financial Disclosures
None reported.

See also

To learn more about pediatric critical care, read "Priority Outcomes in Critically Ill Children: A Patient and Parent Perspective" by Fayed et al in the *American Journal of Critical Care*, 2020;29(5):e94-e103. Available at www.ajconline.org.

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