JPPT | Single-Center Retrospective Study

Evaluation of Institution-Specific Strategy for Converting Dexmedetomidine to Clonidine in a Pediatric Cardiac Intensive Care Unit

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OBJECTIVE This study aimed to evaluate the success and safety of an institution-specific strategy for converting dexmedetomidine to clonidine in the cardiac intensive care unit at a tertiary care pediatric hospital.

METHODS This retrospective descriptive study included pediatric patients under 18 years of age receiving at least 7 days of dexmedetomidine infusion before conversion to clonidine between January 1, 2018, and October 1, 2023. A successful conversion was defined as dexmedetomidine infusion discontinuation in the absence of therapy reinitiation within 36 hours after the initial enteral clonidine dose; no dose increases greater than 15% within 36 hours of initial clonidine dose, and no requirement for supplemental doses. Patients with dexmedetomidine discontinuation before completing stepwise conversion were evaluated for adverse drug events (ADEs). Descriptive statistics were used to analyze the data.

RESULTS A total of 148 episodes of conversion from dexmedetomidine to clonidine were evaluated for 134 patients. Patient demographics and treatment characteristics included a median age at conversion of 4.6 months (IQR, 1.5–7.1), a median duration of dexmedetomidine exposure of 19 days (IQR, 12–34), a median initial clonidine dose of 9.3 mcg/kg/day (IQR, 7.2–10), and a median time to discontinuation of 19 hours (IQR, 17–36) after the first dose of clonidine. Successful conversion occurred in 99 (67%) of episodes evaluated, and no ADEs were identified.

CONCLUSION The conversion allowed for most patients to tolerate the conversion to clonidine, and no ADEs were identified.

ABBREVIATIONS ADE, adverse drug event; CICU, cardiac intensive care unit; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; PICU, pediatric intensive care unit

KEYWORDS clonidine; dexmedetomidine; sedation; pediatric; withdrawal; cardiac intensive care unit

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Introduction

Dexmedetomidine is a centrally acting alpha-2 adrenoreceptor agonist commonly used in intensive care unit (ICU) settings as a sedative, anxiolytic, and analgesic.[1,2] Its use has increased because of its minimal effects on respiratory drive and reduced risk of delirium.[3,4] The Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients with Consideration of the ICU Environment and Early Mobility Guidelines recommend dexmedetomidine as a primary sedative in critically ill pediatric patients requiring mechanical ventilation and in postoperative pediatric cardiac surgery patients to decrease the risk of tachyarrhythmias.[4]

Prolonged intravenous (IV) infusions of dexmedetomidine increase the potential for tolerance and, subsequently, the risk of withdrawal after therapy discontinuation. Withdrawal symptoms include hypertension, tachycardia, diaphoresis, anxiety, fever, and delirium upon abrupt discontinuation.[2,4,5] To facilitate dexmedetomidine discontinuation and decrease the risk of withdrawal, clonidine, an enterally available alpha-2 adrenoreceptor agonist, has been used.[3–9] Reported dosing regimens of clonidine for attenuating withdrawal ranged from 4 to 19 mcg/kg/day, divided every 6, 8, or 12 hours.[6–8] Prior studies also describe inconsistent conversion practices and methods for detecting the impact of clonidine. This variability highlights the need for further research to establish optimal dosing regimens based on patient characteristics, clinical contexts, and safety considerations.

The study institution's pediatric cardiac intensive care unit (CICU) developed a strategy for converting dexmedetomidine infusions to enteral clonidine in

divided doses starting in 2018. At the time of developing this approach, there was no previous literature describing how to do this conversion. Therefore, this practice was developed in close collaboration between CICU pharmacists and physicians, informed by historical experience, physician preference, existing literature, and typical dose ranges and pharmacokinetic properties of both drugs.

The adopted institution-specific strategy for converting a patient from dexmedetomidine to clonidine involves calculating the clonidine dose (mcg/kg/day) by multiplying the rate of dexmedetomidine infusion at the time of conversion (mcg/kg/hr) by 10 (a 1:10 ratio). It is recommended to divide the daily clonidine dose every 6 hours, unless the individual dose falls below the minimum measurable volume set by the institution. Clonidine is administered concomitantly with dexmedetomidine until the fourth dose of clonidine is given. The decision to overlap therapy while decreasing the dexmedetomidine dose was guided by the onset of action of clonidine and the half-lives of clonidine and dexmedetomidine.[5,10,11] This allows clonidine sufficient time to reach therapeutic levels while dexmedetomidine is weaned to discontinuation. For example, dexmedetomidine 1 mcg/kg/hr is converted to enteral clonidine 10 mcg/kg/day divided every 6 to 12 hours. Clonidine is administered in the form of tablets or extemporaneously compounded suspension (0.1 mg/mL). The preferred frequency of clonidine was a daily dose divided every 6 hours unless the volume was less than 0.05 mL (0.005 mg), which is the minimum measurable volume determined by the institution to ensure the accuracy of doses drawn up. To facilitate the conversion from dexmedetomidine to clonidine, the institution-specific strategy recommends that the dexmedetomidine infusion rate be decreased by half 30 minutes after the second and third doses of enteral clonidine and discontinued 30 minutes after the fourth clonidine dose (Table 1).

Table 1. Example of Institution-Specific Strategy for Converting a Dexmedetomidine Infusion to Enteral Clonidine

Example: Dexmedetomidine IV 1 mcg/kg/hr	
Step 1	Administer the first dose of enteral clonidine 10 mcg/kg/day divided every 6–12 hr
Step 2	Decrease dexmedetomidine IV rate to 0.5 mcg/kg/hr 30 min after administering second dose of enteral clonidine
Step 3	Decrease dexmedetomidine IV rate to 0.25 mcg/kg/hr 30 min after administering third dose of enteral clonidine
Step 4	Discontinue dexmedetomidine IV 30 min after the fourth dose of enteral clonidine

IV, intravenous

This study aimed to address the gaps in current literature by focusing on patients converted to clonidine using this standardized conversion approach and outlining specific criteria for achieving successful conversion. The purpose of this study was to describe the conversion of dexmedetomidine to clonidine to evaluate the success and tolerability of this institution-specific strategy.

Materials and Methods

This retrospective descriptive study was performed at a 600-bed freestanding children's hospital with a 36-bed CICU. Patients were identified for inclusion if they had orders for dexmedetomidine and clonidine between January 1, 2018, and October 1, 2023. Patients less than 18 years of age, admitted to the CICU, who received dexmedetomidine infusions for at least 7 days and were converted to clonidine using the institution-specific strategy, were included. Patients were excluded if they were administered any alpha-2 adrenoreceptor agonists (i.e., clonidine or guanfacine) as a maintenance medication before dexmedetomidine initiation, received an initial clonidine dose that deviated greater than 15% of the calculated dose, were intubated at the time of conversion, received extracorporeal membrane oxygenation and/or continuous renal replacement therapy, became nothing by mouth status and could not receive enteral medications within 36 hours of the initial dose of clonidine and/or were transferred to another facility at the time of conversion (to account for any missing information that may occur outside the institution), or expired within 36 hours of the initial dose of clonidine. Patients with greater than 1 conversion episode were included in this evaluation.

Baseline demographic data, including age and weight at the time of conversion, sex, and race, were collected. Data related to treatment characteristics, including the number of episodes, initial and maximum dexmedetomidine infusion rate (mcg/kg/hr), total dexmedetomidine infusion duration (days), dexmedetomidine infusion rate at the time of conversion (mcg/kg/hour), clonidine dose at time of conversion (mcg/kg/day), time between the administration of the first dose of clonidine and dexmedetomidine discontinuation (hours), were collected.

The primary endpoint was the rate of successful conversion from dexmedetomidine to clonidine, defined as: (1) dexmedetomidine infusion discontinuation within 36 hours of the initial clonidine dose, (2) lack of dexmedetomidine infusion restart within 36 hours after infusion discontinuation, (3) absence of clonidine dose adjustments greater than 15% of the recommended dose within 36 hours of initial clonidine dose given, and (4) no requirement for supplemental intermittent

doses of dexmedetomidine or clonidine within 36 hours of initial clonidine dose.

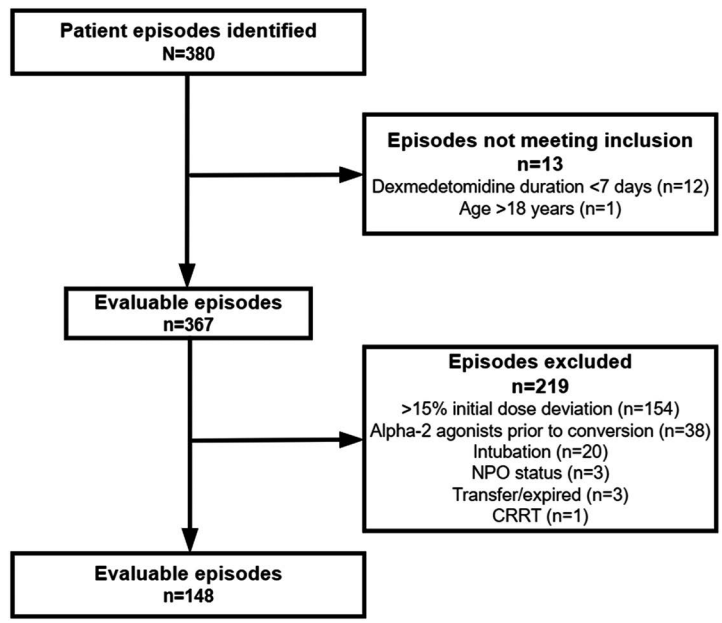
The secondary endpoint was the safety of this conversion strategy, focusing on the number of adverse drug events (ADEs) that occurred during conversion. The 2 ADEs of interest were hypotension and bradycardia that occurred as a result of the conversion. To assess this, the institution's internal safety reporting system was reviewed for any reported ADEs linked to the conversion. Hospital staff are trained to recognize and report ADEs using a standardized definition, which classifies an ADE as any harm experienced by a patient as a result of medication exposure.[12] Acknowledging that only 10% to 20% of these events are likely reported, steps were taken to ensure ADEs potentially associated with this conversion were captured.[13] If the patient, after receiving at least 1 dose of clonidine following conversion, subsequently had their clonidine therapy discontinued or its dose reduced within 36 hours of the initial clonidine dose, or if dexmedetomidine was discontinued within 18 hours of the initial clonidine dose, further investigation to assess for possible ADEs as causation for deviation from the standard conversion protocol was completed. This assessment included reviewing the attending physician's daily progress notes for any mention of common ADEs related to conversion, using keywords of bradycardia and/or hypotension. Vital signs during conversion were also examined to determine whether patients experienced bradycardia or hypotension, defined as any occurrences in which the patient's measured vital sign fell below the normal age-related values as specified by the institution.

Descriptive statistics were used to analyze the data, with nominal data expressed as a percentage and continuous data expressed as median with IQR. A Shapiro-Wilks test was performed on all continuous data to test for normality.

Results

A total of 134 patients with 148 episodes of conversion from dexmedetomidine to enteral clonidine were evaluated (Figure 1). Thirteen patients experienced more than one conversion episode, with 12 having 2 episodes, and 1 patient having 3 episodes. The Shapiro-Wilks test demonstrated significant departure from normality for all continuous data points ($p > 0.05$). For baseline demographics (Table 2), the median age at conversion was 4.6 months (IQR, 1.5–7.1), the median weight at conversion was 4.7 kg (IQR, 3.5–6.7), 72 (54%) patients were male sex at birth, and 76 (56.7%) of the patients were White or Caucasian. The median duration of dexmedetomidine exposure before conversion was 19 days (IQR, 12–34). The median dexmedetomidine infusion rate at the time of the conversion to clonidine was 1 mcg/kg/hr (IQR, 0.7–1) at the time of conversion to clonidine. The median initial clonidine dose at conversion was 9.3 mcg/kg/day (IQR, 7.2–10) and was administered at a frequency of every 6 hours for 135 (91%) of episodes. Dexmedetomidine was discontinued a median of 19 hours (IQR, 17–36) following administration of the first dose of clonidine. Information

Figure. CONSORT diagram. *CRRT, continuous renal replacement therapy, NPO, nothing by mouth.*



regarding the remaining treatment characteristics is available in Table 3.

Of the total 148 episodes evaluated, 99 (67%) met the conditions for successful conversion. Episodes may have had more than 1 reason qualifying for unsuccessful conversion, and the total of each reason is displayed in Table 4. In 76 episodes where dexmedetomidine was infused for less than the median of 19 days, 23 (30%) resulted in unsuccessful conversions. In comparison, 72 episodes with infusions lasting more than 19 days had 26 (36%) unsuccessful conversions. In 31 patients, dexmedetomidine was discontinued within 18 hours of the initial clonidine dose, which prompted a review for any ADEs. Clonidine was neither discontinued nor dose-reduced because of ADEs within 36 hours of its initiation. No ADEs were reported during the study period.

Table 2. Baseline Demographics

Total Patients		**N = 134**
Male sex, n (%)		72 (54)
Age at conversion, mo, Median (IQR)*		4.6 (1.5–7.1)
Weight at conversion, kg, Median (IQR)*		4.7 (3.5–6.7)
Race† n (%)	White or Caucasian	76 (56.7)
	Unknown	29 (21.6)
	Black or African American	25 (18.7)
	Asian	2 (1.5)
	Hispanic or Latino White	2 (1.5)

* Total number of episodes: 148.
† As documented in the electronic health record.

Table 3. Treatment Characteristics for Conversion From Dexmedetomidine to Clonidine

Total Episodes N = 148	
Total dexmedetomidine treatment duration, days	19 (12–34)
Initial dexmedetomidine rate, mcg/kg/hr	0.5 (0.3–0.5)
Maximum dexmedetomidine rate, mcg/kg/hr	1.2 (1–1.5)
Dexmedetomidine rate at time of conversion to clonidine, mcg/kg/hr	1 (0.7–1)
Initial clonidine dose, mcg/kg/day	9.3 (7.2–10)
Initial clonidine frequency, n (%)	Every 6 hours: 135 (91) Every 8 hours: 8 (5) Every 12 hours: 5 (3)
Time between clonidine initiation and dexmedetomidine discontinuation, hr	19 (17–36)

Nonparametric continuous data presented as median (IQR); nominal data presented as n, (%)

Discussion

This study aimed to assess the success and safety of an institution-specific conversion strategy from dexmedetomidine to clonidine used within the CICU. The decision to restrict to this patient population was driven by the fact that the conversion practice described is specific to the CICU at the study institution and aimed to minimize variability in the patient population. The motivation behind conversion to enteral clonidine is to facilitate de-escalation from ICU-level care by allowing for expedited discontinuation of dexmedetomidine infusions, while minimizing the risk of withdrawal symptoms. Although previous studies have investigated the role of clonidine for attenuating withdrawal symptoms in patients transitioning from dexmedetomidine, these studies do not focus on CICU patients, there is variability in dosing recommendations, and limited consensus on the most effective approach.[5–9]

Liu et al[6] conducted a retrospective analysis involving 24 episodes of converting dexmedetomidine to clonidine in patients admitted to a pediatric intensive care unit (PICU) rather than in CICU patients evaluated in the present study. In contrast to the present

Table 4. Dexmedetomidine to Clonidine Conversion Effectiveness

Total Episodes N = 148	
Successful conversion, n (%)	99 (67)
Counts of Individual Reasons for Unsuccessful Conversion, n = 64*	
Dexmedetomidine continuation for >36 hr following clonidine initiation, n (%)	35 (55)
Scheduled clonidine dose increased (>15% of recommended dose) within 36 hr of dexmedetomidine discontinuation, n (%)	19 (30)
As needed clonidine rescue administration within 36 hr of clonidine initiation, n (%)	7 (11)
Dexmedetomidine restarted within 36 hr of clonidine initiation, n (%)	3 (5)

* Unsuccessful conversion may occur for >1 reason per episode.

study, where the dexmedetomidine rate determined the dose of clonidine, the enteral clonidine dose was based on age, with 8 mcg/kg/day for patients younger than 6 months of age or 16 mcg/kg/day for patients 6 months and older. The stepwise conversion approach in the current study was similar to the approach used in the study, but dexmedetomidine was discontinued after the third dose rather than the fourth. The median dexmedetomidine treatment duration was 3.8 days, which is shorter than the median 19 days in the present study. Eight conversion episodes (33%) demonstrated withdrawal that required additional support during conversion, similar to the proportion of episodes requiring additional sedation in the present study. The median overlap of clonidine and dexmedetomidine was 18.2 hours, which is comparable to the overlap observed in the present study. Additionally, 2 episodes (8%) had bradycardia or hypotension requiring intervention.

Another analysis by Lee et al[7] evaluated 39 conversion episodes from dexmedetomidine to clonidine in patients admitted to the PICU. The median dexmedetomidine duration was 7.6 days, which is less than half of the median duration observed in this evaluation. Unlike the institution in the current study, there was no standardized conversion practice. The median initial clonidine dose was 7.8 mcg/kg/day and was typically given every 8 or 12 hours. Of note, 5% of episodes were converted using transdermal clonidine which was not employed in the present study. Similar to the present study, the conversion from dexmedetomidine to clonidine occurred over a median of 19.2 hours. In terms of outcomes, 14 (37%) conversion episodes resulted in elevated Withdrawal Assessment Tool (Version 1) scores of 3 or greater. However, only 7 (18%) in their study required an increase in sedation, compared with the higher intervention rate observed in the present study, which could be attributed to the shorter duration of dexmedetomidine exposure. Additionally, adverse cardiovascular events attributed to conversion occurred in 4 patient episodes (10%).

Crabtree et al[8] conducted a study involving 105 PICU patients who received dexmedetomidine infusions for at least 24 hours, with clonidine administered within 72 hours of discontinuation of dexmedetomidine. Unlike the present study, which did not collect data on other sedatives, their study excluded patients receiving other continuous infusion sedatives besides dexmedetomidine. A notable difference in their approach was that not all patients were converted with dexmedetomidine, which overlapped with clonidine. For those with dexmedetomidine infusion exceeding 5 days, enteral clonidine was initiated at 15 mcg/kg/day, divided every 8 hours, rather than the approach in the present study, where the clonidine dose was scaled to the dexmedetomidine rate at the time of clonidine initiation. Although both the present and Crabtree et al[8] study used a stepwise conversion process, dexmedetomidine was discontinued after the second dose compared with the fourth dose in the present study. The median cumulative duration of dexmedetomidine infusion in this group was 5.5 days, approximately one-third the duration in this study. This may explain, in part, why withdrawal symptoms requiring modifications to the planned conversion occurred in only 12 (18%) of patients rather than the 33% of episodes requiring additional support during conversion in this evaluation.

By adhering to the conversion practice used in this study's CICU, dexmedetomidine should be discontinued 30 minutes after the fourth dose of clonidine. This should occur between 18 and 36 hours after the first dose of clonidine, depending on the frequency of clonidine administration. Therefore, a period of 36 hours for dexmedetomidine discontinuation was chosen as a condition for conversion success providing sufficient time to complete the conversion and allowing for additional buffer time to account for medical rounds, ordering and verification, medication preparation, and administration.

The use of strict inclusion and exclusion criteria played a role in controlling for potential confounding variability for the conversion process. It is noteworthy that episodes were excluded most frequently for an initial clonidine dose deviation greater than 15% from the standard conversion guidance. This dose deviation threshold was chosen to help ensure accuracy of volume measurement based on syringe size and associated barrel graduations in conjunction with dose rounding logic within the institution's computerized physician order entry system. Patients intubated at the time of conversion were excluded because they had a higher likelihood of receiving other sedatives to facilitate mechanical ventilation. Typically, other sedatives are rapidly weaned in preparation for extubation, which is why episodes in intubated patients were excluded. Patients on extracorporeal membrane oxygenation and/or continuous renal replacement therapy were excluded as a measure to prevent potential confounding effects due to pharmacokinetic impact from any extracorporeal circuitry.

This evaluation found that most episodes were successfully converted from dexmedetomidine to clonidine according to the predefined criteria. This indicates that the conversion practice used in this study is clinically feasible by achieving the intended therapeutic goal of dexmedetomidine discontinuation. The absence of ADEs identified among episodes included is reassuring and underscores the safety profile of our conversion practice.

The remaining episodes that did not meet the criteria for successful conversion required additional support during the conversion process, such as extended dexmedetomidine infusion, dose increases

of clonidine, or rescue doses of either clonidine or dexmedetomidine. This can be compared with the studies detailed above, where 18% to 33% of patients required modification or an increase in sedation during conversion.[6–8] It is noteworthy that episodes in this study had greater dexmedetomidine exposure than previously reported.

This study has limitations, including an absence of a comparator group and data on other sedatives used at the time of conversion. Details regarding the reason for admission or specific cardiac defects were not collected because of feasibility concerns. Patients at the study institution's CICU often have complex surgical histories, resulting in a heterogeneous patient population that would have been difficult to categorize. Although collecting information on the concomitant administration of other sedatives would help limit the confounding of the effects of this conversion, excluding patients who were intubated at the time of conversion ensured that the patients evaluated were less likely to have undergone significant changes to sedation at the time of conversion. Information on other medications that may impact blood pressure was not collected. However, given this retrospective review was of patients in a CICU, the use of such medications could have confounded the assessment of hemodynamics.

It is also important to note that in practice, this conversion would not be attempted unless the patient were clinically stable for at least 24 hours and not experiencing significant withdrawal or excessive sedation requiring active titration of concomitant sedatives. Given that data collection was retrospective and the safety reporting system is voluntary, there is a potential for underdetection or underreporting of ADEs.[13] Data on dexmedetomidine use at other facilities could not be reliably reported for patients started before transfer to the study institution. Therefore, dexmedetomidine exposure was only reflective of what was administered at the study institution.

Additionally, there is variability and subjectivity to the elements of withdrawal, which cannot be adequately accounted for retrospectively. Differences in provider preferences for conversion and weaning strategies may explain why a significant number of episodes were excluded because of dose deviations. This variability in practice may also introduce bias, as successful conversions may not have been captured due to deviations from the guidance provided by the institution-specific conversion strategy.

Conclusion

The conversion practice investigated allowed for most patients to tolerate the transition from a dexmedetomidine infusion to clonidine, and no ADEs were identified. Future studies should assess the safety and efficacy of converting from dexmedetomidine to clonidine.

Article Information

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