Evaluating the transition from dexmedetomidine to clonidine for agitation management in the intensive care unit

Kimberly Terry¹, Rachel Blum² and Paul Szumita³

Abstract

Objectives: Limited literature exists examining the use of enteral clonidine to transition patients from dexmedetomidine for management of agitation. The aim of this study was to evaluate dexmedetomidine discontinuation within 8 h of enteral clonidine administration in addition to the rates of dexmedetomidine re-initiation in patients who failed clonidine transition.

Methods: A single-center, retrospective analysis evaluated critically ill adult patients from 1 February 2013 to 28 February 2014, who used dexmedetomidine and clonidine for sedation management. Patients were excluded if they received enteral clonidine for reasons other than sedation management. Secondary aims of the study observed time to dexmedetomidine discontinuation, agitation (Richmond Agitation Sedation Scale) and delirium ratings (Confusion Assessment Method for the intensive care unit), clonidine dose, and enteral clonidine discontinuation.

Results: In all, 26 patients were evaluated. Demographics included a mean age of 54.4 (±16.7) years, Acute Physiology and Chronic Health Evaluation II score of 18 (interquartile range = 14–22), and 80.7% of admissions to the cardiac surgery intensive care unit. Dexmedetomidine discontinuation occurred in 17 (65.4%) patients within 8 h of receiving clonidine. The total median clonidine exposure per intensive care unit day was 0.35 mg/ICU day (interquartile range = 0.2–0.5) in patients who discontinued dexmedetomidine within 8 h and 0.5 mg/ICU day (interquartile range = 0.4–1.0) (p = 0.036) in patients who did not. We observed similar Richmond Agitation Sedation Scale and Confusion Assessment Method for the intensive care unit scores and rates of hypotension. Unintentional use of clonidine beyond ICU and hospital stay was observed in 54% and 23% of patients, respectively.

Conclusion: Enteral clonidine may be an effective and safe alternative to transition patients off of dexmedetomidine for ongoing sedation management. Clinicians should critically evaluate the need for clonidine at ICU and hospital discharge. More studies comparing the use of clonidine to transition from dexmedetomidine infusions are needed.

Keywords
Critical care, sedation, clonidine, dexmedetomidine

Introduction

The presence of agitation and delirium in critically ill patients is associated with adverse clinical outcomes and may contribute to prolonged time on mechanical ventilation, impaired cognition, and increased hospital and intensive care unit (ICU) length of stay.¹⁻⁴ Additional adverse outcomes may include self-extubation and unintentional removal of medical devices, post-traumatic stress, nosocomial infections, and increased economic and psychological burden for caregivers.⁵⁻⁷

¹Department of Pharmacy, University of Utah Hospital, Salt Lake City, UT, USA
²Department of Pharmacy, South Shore Hospital, South Weymouth, MA, USA
³Department of Pharmacy, Brigham and Women’s Hospital, Boston, MA, USA

Corresponding author:
Kimberly Terry, Department of Pharmacy, University of Utah Hospital, 50 North Medical Drive, Rm A-050, Salt Lake City, UT 84132, USA.
Email: kimberly.jacob@utah.edu

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The 2013 Society of Critical Care Medicine practice guidelines recommend a benzodiazepine-sparing approach to manage sedation in ICU patients. This recommendation is likely based on studies associating benzodiazepines with increased time on mechanical ventilation compared to non-benzodiazepine therapy. Propofol or dexmedetomidine is used in clinical practice as established benzodiazepine-sparing strategies; however, several other non-medications specific strategies including targeting light sedation, implementation of a protocol of frequent and routine assessment, sedation interruption, bolus rather than infusion, and analgosedation strategies have all lead to important clinical endpoints such as decrease in time on mechanical ventilation.

Dexmedetomidine, an intravenous (IV) alpha-2A adrenergic agonist (A2A), provides sedative effects and is often used for the management of pain, agitation, and delirium in critically ill patients. Dexmedetomidine was approved by the Food and Drug Administration (FDA) as a sedative agent limited to a 24-h duration; however, in clinical practice, the length of infusion often exceeds 24 h. Its characteristics include arousable sedation with minimal effects on respiratory function, but may cause hypotension and bradycardia. Clonidine, with a similar mechanism of action, may be an alternative enteral agent to transition patients from dexmedetomidine for sedation management. The use of enteral clonidine for continued sedation may facilitate the transfer out of an ICU by decreasing the need for a titrated IV sedative while promoting the use of enteral routes of medication administration and decreasing costs associated with IV medications. The purpose of our study was to assess the efficacy and safety of transitioning patients from dexmedetomidine to enteral clonidine for sedation management in the ICU.

Methods and materials

Approval was granted by the Partners Healthcare Institutional Review Board. In this single-center, retrospective analysis, we evaluated critically ill adult patients admitted to the ICU from 1 February 2013 to 28 February 2014 who received clonidine to transition from dexmedetomidine for ongoing sedation management. All patients >18 years of age located within our institutions; seven ICUs (~90 beds), each with 2:1 or 1:1 nursing care, were identified for inclusion using a clonidine and analgosedation strategy. Patient demographics (age, gender, co-morbidities, and Acute Physiology and Chronic Health Evaluation II (APACHE II)) and reason for ICU admission were recorded from patient’s individual admission history.

Safety endpoints evaluated the occurrence of the following hemodynamic parameters (presence of arrhythmia, mean arterial pressure (MAP) <65 or >90, heart rate (HR) <50 or >110, and systolic blood pressure (SBP) <90) between the DC and nDC groups during clonidine transition until clonidine discontinuation. Unintended continuation of clonidine in the ICU and at hospital discharge in all patients was also recorded.

Patient demographics

Demographic data (age, gender, co-morbidities, and Acute Physiology and Chronic Health Evaluation II (APACHE II)) and reason for ICU admission were recorded from patient’s individual admission history.
Statistics
Due to limited literature describing typical rates of dexmedetomidine discontinuation upon clonidine initiation, a 70% transition rate within 8 h was defined as successful a priori. Non-normally distributed continuous variables were reported as median (interquartile range (IQR)) and were compared using the Mann–Whitney U test, where applicable. Categorical data comparisons used the chi-square test, and statistical significance was defined as $p \leq 0.05$. Based on the retrospective nature of the study, with an unknown population of patients using enteral clonidine from either historical data or literature at the time of study design, sample size calculations were not performed.

Results
During our study period, a total of 42 patients were identified, while 16 patients met the exclusion criteria. One patient was excluded for using a non-enteral form of clonidine while 15 patients used enteral clonidine for documented indications other than dexmedetomidine transition and sedation management. Twenty-six patients were included in the final analysis, predominantly cardiac surgery ICU patients with cardiac-related co-morbidities (Table 1). Four patients were mechanically ventilated at the time of study inclusion.

In the cardiac surgery population, dexmedetomidine was widely used for post-cardiac procedural sedation. Dexmedetomidine use in our non-cardiac surgery population was utilized primarily for additional sedation and agitation requirements; however, reason for agent selection was not well documented.

Clonidine transition
The transition from dexmedetomidine to enteral clonidine is not protocolized or widely implemented in our institution. Patients who transitioned to clonidine were predominantly stable from their initial ICU admission, had enteral access with IV dexmedetomidine as a barrier to transition out of the ICU. Clonidine tablets were administered orally or crushed and administered through an enteral feeding tube. Initiating clonidine was performed on a patient-by-patient basis by the discretion of the attending and primary team. Initial clonidine doses were 0.1 mg in most patients and titrated up for sedative effect every 6–8 h until hemodynamic changes prohibiting further titration or sedative goals were met using RASS.

Major endpoints
Dexmedetomidine was discontinued in 17 (65.4%) patients within 8 h of clonidine administration, narrowly missing our definition of a successful transition. In addition, dexmedetomidine was not restarted in any patient for documented clonidine failure. Patients who successfully transitioned within 8 h had a median transition time of 1 h (IQR = 0.5–4.25), while patients who did not had a median transition time of 28 h (IQR = 20–56.5). Patients who failed to transition within 8 h included those with alcohol withdrawal, septic shock, endocarditis, lung transplant, and aortic valve replacement.

Minor endpoints
The majority of patients in the DC group transitioned successfully within 4 h, 13 (76.5%), while the majority of

Table 1. Demographic data.

| Variables                      | N=26   |
|-------------------------------|--------|
| Age, mean (SD), years         | 54.4 (16.9) |
| Male, n (%)                   | 17 (63.0) |
| APACHE II score, median (IQR) | 18 (14–22) |
| BMI, mean (SD), kg/m²         | 32 (4.1) |
| Co-morbidities, n (%)         |        |
| Hypertension                  | 14 (51.9) |
| Hyperlipidemia                | 13 (48.1) |
| Alcohol and/or substance abuse| 10 (37.0) |
| Diabetes                      | 6 (22.2)  |
| Anxiety disorder              | 4 (14.8)  |
| Depression                    | 3 (11.1)  |
| Hypothyroidism                | 3 (11.1)  |
| Morbid obesity                | 3 (11.1)  |
| Oncologic history             | 3 (11.1)  |
| Congenital heart disorder     | 2 (7.4)   |
| CHF                           | 2 (7.4)   |
| BPH                           | 2 (7.4)   |
| Mechanical ventilation        | 4 (14.8)  |
| ICU, n (%)                    |        |
| Cardiac surgery               | 21 (80.7) |
| Thoracic                      | 3 (11.5)  |
| Neurology                     | 1 (3.8)   |
| Surgical                      | 1 (3.8)   |
| Reason for ICU admission      |        |
| Coronary artery bypass graft  | 7 (26.9)  |
| AVR                           | 5 (19.2)  |
| Endocarditis                  | 5 (19.2)  |
| Lung transplant               | 2 (7.7)   |
| PE                            | 1 (3.8)   |
| Aortic dissection             | 1 (3.8)   |
| CAD                           | 1 (3.8)   |
| VAD                           | 1 (3.8)   |
| Radical pleurectomy           | 1 (3.8)   |
| Trauma                        | 1 (3.8)   |
| Alcohol withdrawal            | 1 (3.8)   |
| ICU LOS, median (IQR)         | 8 (4–10.5) |
| Hospital LOS, median (IQR)    | 12.5 (7–28) |
| ICU mortality, n (%)          | 0        |
| Hospital mortality, n (%)     | 0        |

SD: standard deviation; IQR: interquartile range; APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; CHF: congestive heart failure; BPH: benign prostatic hyperplasia; ICU: intensive care unit; AVR: aortic valve repair; PE: pulmonary embolism; CAD: coronary artery disease; VAD: ventricular assist device; LOS: length of stay.
patients in the nDC group took longer than 24 h, 6 (66.7%) (Table 2). We observed a median RASS score of 0 in both DC and nDC groups with similar rates of positive CAM-ICU scores. Rescue sedatives primarily used were opioids, benzodiazepines, and antipsychotics independently and in combination (Table 3). Sixteen of 17 patients (94%) in the DC group used rescue sedation while 9 of 9 patients (100%) in the nDC group used rescue sedation (Table 3). The total median clonidine exposure per ICU day was significantly different between the DC and nDC groups at 0.35 mg/ICU day (IQR = 0.2–0.5) and 0.5 mg/ICU day (IQR = 0.4–1.0) (p = 0.036), respectively (Table 3). Additionally, the median clonidine exposure per ICU day was significantly different between the DC and nDC groups, respectively.

### Table 2. Time to dexmedetomidine discontinuation.

| Time (h) | DC (n = 17) | nDC (n = 9) |
|----------|-------------|-------------|
| 0–4      | 13          | –           |
| 5–8      | 4           | –           |
| 9–12     | –           | –           |
| 13–16    | –           | –           |
| 17–24    | –           | 3           |
| 24+      | –           | 6           |

DC: patients who discontinued dexmedetomidine within 8 h of clonidine administration; nDC: patients who did not discontinue dexmedetomidine within 8 h of clonidine administration.

**Discussion**

Our study evaluated the efficacy and safety of using clonidine to transition patients from dexmedetomidine for ongoing sedation management where minimal literature exists. The literature describing this practice is limited to a single prospective observational study describing the use of clonidine to transition from dexmedetomidine.22 We observed a modest discontinuation rate of dexmedetomidine within 8 h after clonidine administration, narrowly missing our 70% discontinuation goal. Recent data suggest that clonidine may be effective in the transition from dexmedetomidine in 75% of patients within a 48 h time frame.22 Although our transition rates were assessed in a shorter time period of 8 h, our results support the findings of this study suggesting that clonidine may be a viable enteral agent when considering prolonged A2A use for ongoing sedation management.

Our institution’s dexmedetomidine stewardship program provides guidance for the utilization of dexmedetomidine at initiation.21 If dexmedetomidine use is warranted beyond 24 h, the stewardship program, in concert with the team, evaluates the individual patients’ sedation goals. The practice of using clonidine to transition from dexmedetomidine has not been protocolized within or outside our stewardship program.24-27,29

A large majority of our patient cohort was from the cardiac ICU with multiple cardiac-related co-morbidities. Use of enteral clonidine in this patient population has limited evidence; however, the use of IV clonidine has been evaluated in studies conducted outside the United States. In patients with post-cardiac surgery for type A aortic dissection, IV clonidine has been shown to improve respiratory function and shorten mechanical ventilation and ICU length of stay versus placebo.30 In this analysis, patients treated with clonidine also demonstrated lower delirium detection scores and shorter neurological recovery time. These authors considered the useful adjuvant properties of clonidine such as sedative effects, reduction in opioid dosage, and alleviation of withdrawal symptoms as reasons for better neurological and delirium outcomes with clonidine use.30

A greater number of patients who discontinued dexmedetomidine within 8 h had infusion rates less than or equal to 0.4 µg/kg/h. Thirteen of 17 patients in the DC group had stopped dexmedetomidine within 4 h of clonidine administration of which 9 discontinued before the first hour. The practice of discontinuing dexmedetomidine at or near the time of clonidine administration highlights the variation in practice among primary teams. The nDC group had higher dexmedetomidine infusion rates and clonidine doses may not have been optimized in this group. Patients in both the DC and nDC groups had similar median RASS and CAM-ICU scores and similar use of rescue sedation. Use of enteral clonidine has shown to reduce the co-administration of other sedative agents such as benzodiazepines and provide analgesia.31

In a study by Gagnon et al., clonidine doses of 0.3 mg every 6 h were optimal to transition patients from higher dexmedetomidine rates of 1.0 µg/kg/h.22 Starting doses of clonidine within our cohort were primarily 0.1 mg three times a day (TID) and titrated on a dose-by-dose basis dependent on hemodynamic response and sedation documentation. This may explain the increased time needed to transition patients on higher infusion rates to clonidine than those starting at lower infusion rates. Dexmedetomidine was weaned as soon as patients were responding to clonidine with appropriate RASS, CAM-ICU documentation, and hemodynamic changes. No specific protocols were established for increasing clonidine doses, or decreasing dexmedetomidine infusion rates; however, a single prospective study suggests that doses of 0.3 mg four times a day may be an effective starting dose for higher dexmedetomidine infusion rates.22

Hemodynamic events were not statistically different between the DC and nDC groups; however, hypotension
occurred at 29.4% and 44.4%, respectively. Hypotension, an unintended, but common manifestation, can occur in a variety of different settings. In an analysis of patients treated with clonidine or placebo for non-cardiac surgery with the primary outcome of composite death or myocardial infarction, patients who used clonidine had higher rates of clinically significant hypotension (47.6% vs 37.1%, \( p \leq 0.001 \)).

Utilization of higher clonidine doses reaching elevated plasma concentrations of 1.5 ng/mL may stimulate peripheral alpha-1 adrenergic receptors, preserving blood pressure, whereas lower doses have been associated with significant hypotension in non-cardiac surgery patients. Although our patient population consisted primarily of cardiac surgery patients, these findings may explain our increased rates of hypotension in lower clonidine doses. In addition, in a study by Srivastava et al., hypotension rates were 31% and 9% (\( p = 0.01 \)), comparing IV clonidine and dexmedetomidine for short-term sedation, respectively. Although our patient populations differed, we observed similar rates of hypotension in both cohorts, but were not statistically significant. IV clonidine is not used in the United States for sedation; however, it may be a viable alternative in the indicated regions.

The process of weaning enteral clonidine when sedation was no longer indicated was not studied in this cohort; however, this practice may need to be employed to reduce adverse events from rapid withdrawal of clonidine. Previous literature suggests that weaning clonidine by slowly increasing the dosing interval may reduce the occurrence of clonidine withdrawal.

Less than half of the patients discontinued clonidine at ICU transfer and nearly a quarter of patients had clonidine listed as a hospital discharge medication. In an observational study evaluating medication discontinuation after ICU stay, 87% of medications initiated during ICU stay were continued without an indication and 65% continued after hospital discharge. Adding a process for appropriate weaning and discontinuation of clonidine for ICU sedation will need to be addressed in future patient transition processes.

There are several limitations due to the observational, retrospective, and single-center design. It is difficult to determine the clinical impact of negative hemodynamic events as this was not measured long term. Lacking a matched comparator group, our analysis is purely observational and efficacy and safety outcomes cannot be confidently extrapolated. Our study did not examine pharmacoeconomic impacts of using an enteral versus IV A2A; however, utilizing clonidine may provide large cost avoidance. Gagnon et al. estimated a cost savings from US$15,000 to US$52,000 of drug acquisition costs from their patient cohort based on the duration of clonidine therapy after dexmedetomidine cessation in the ICU for the 3-month pilot period. Drug costs may be a limitation for some institutions to support prolonged dexmedetomidine use, making clonidine a more economical replacement agent.

Additionally, our institution lacks overall guidance for appropriate patient selection and transition practice to enteral clonidine from dexmedetomidine. This variability in practice was evident with a large number of patients discontinued from dexmedetomidine at the time of clonidine administration. Variability in practice without the use of guidelines makes identification of all potential patients difficult to acquire and replication of transition was not possible for this

### Table 3. Minor endpoints.

| Minor endpoints | DC (n = 17) | nDC (n = 9) | p-value |
|-----------------|------------|------------|---------|
| RASS median (IQR) | 0 (0–2) | 0 (−2 to 2) |         |
| CAM-ICU positive, n (%) | 3 (17.6) | 4 (44.4) |         |
| Total CLON exposure, mg/ICU day, median (IQR) | 0.35 (0.2–0.5) | 0.5 (0.4–1.0) | 0.036 |
| CLON exposure in first 8 h, mg, median (IQR) | 0.1 (0.1–0.2) | 0.1 (0.1–0.15) | 1.0     |
| DEX rate \( \leq 0.4 \mu g/kg/h, n (%) | 15 (88.2) | 2 (22.2) | 0.0016  |
| DEX rate at CLON initiation, \( \mu g/kg/h \) (IQR) | 0 (0–2.5) | 0.7 (0.45–0.7) | 0.005   |
| DEX duration prior to CLON (h), median (IQR) | 24 (14.5–39) | 13 (4–32) | 0.14    |
| CLON initiation dose, mg, median (IQR) | 0.1 (0.1–0.2) | 0.1 (0.1–0.15) | 0.8     |
| CLON duration days, median (IQR) | 2 (1–4.5) | 3 (2–5) | 0.55    |
| Rescue sedation, n (%) | 16 (94) | 9 (100) |         |
| Opioid only, n | 11 | 3 |         |
| BZD only, n | 1 | 0 |         |
| Antipsychotic only, n | 2 | 0 |         |
| Opioid + BZD, n | 0 | 3 |         |
| Opioid + antipsychotic, n | 1 | 1 |         |
| BZD + antipsychotic, n | 0 | 2 |         |
| Opioid + BZD + antipsychotic, n | 1 | 0 |         |

DC: patients who discontinued dexmedetomidine within 8h of clonidine administration; nDC: patients who did not discontinue dexmedetomidine within 8h of clonidine administration; RASS: Richmond Agitation Sedation Scale; IQR: interquartile range; CAM-ICU: confusion assessment method in the intensive care unit; CLON: clonidine; DEX: dexmedetomidine; BZD: benzodiazepine.
study. Comparisons between the use of rescue sedation doses and other concomitant medications were missing from the data collection and may have provided additional practice considerations when transitioning patients from dexmedetomidine to clonidine in the ICU. Additionally, RASS and CAM-ICU documentation were not evaluated critically and may not have been a true reflection of our populations’ agitation and delirium status. Due to the number of limitations and variability, the observations reported in this study should be evaluated critically and may only provide insight for future confirmatory studies.

Conclusion

Clonidine may be an effective and safe alternative to transition patients off of dexmedetomidine for management of sedation and may reduce the duration of dexmedetomidine infusions. Clinicians should critically evaluate the need for clonidine at ICU and hospital discharge. Future prospective studies are needed to compare the efficacy and safety of transitioning from dexmedetomidine to clonidine in a protocolized manner for sedation management.

Declaration of Conflicting Interests

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Informed consent

Informed consent was not sought for the present study because of the retrospective nature/chart review design.

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