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

Kimberly Terry[1], Rachel Blum[2] and Paul Szumita[3]

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

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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]

[1]Department of Pharmacy, University of Utah Hospital, Salt Lake City, UT, USA
[2]Department of Pharmacy, South Shore Hospital, South Weymouth, MA, USA
[3]Department 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

The 2013 Society of Critical Care Medicine practice guidelines recommend a benzodiazepine-sparing approach to manage sedation in ICU patients.[8] This recommendation is likely based on studies associating benzodiazepines with increased time on mechanical ventilation compared to non-benzodiazepine therapy.[9–13] Propofol or dexmedetomidine is used in clinical practice as established benzodiazepine-sparing strategies; however, several other non-medication 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.[3,5,9–16]

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.[17] 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.[18–20] Its characteristics include arousable sedation with minimal effects on respiratory function, but may cause hypotension and braydcardia.[21–24] Clonidine, with a similar mechanism of action, may be an alternative enteral agent to transition patients from dexmedetomidine for sedation management.[22] 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 dexmedetomidine usage report from the electronic medical records. Adult patients in the ICU were included in the study if they were initiated on dexmedetomidine and received at least one dose of enteral clonidine with the purpose of sedation management. Patients were excluded if they were administered a non-enteral form of clonidine or were administered clonidine for a purpose other than sedation management.

Sedation strategies vary among each ICU within our institution; however, propofol is the preferred continuous infusion sedative. Dexmedetomidine use is approved using the guidance of an institutional dexmedetomidine stewardship program. Our ICUs consist of both open and closed units with 24-h intensivist coverage. The provider along with the stewardship program evaluates a patient's sedation goals and reassesses the need for dexmedetomidine, particularly for use beyond the FDA-approved 24 h. Using the Richmond Agitation Sedation Scale (RASS), monitored every 2–8 h and the Confusion Assessment Method for the ICU (CAM-ICU), monitored every 8 h, patients are routinely assessed for the depth of sedation and symptoms of delirium. Pain scores within our institution utilize both the numeric rating scale for responsive patients and the Critical Pain Observation Tool (CPOT) for non-responsive patients. Focusing primarily on sedation management and the transition from IV to enteral pharmacotherapy, RASS and CAM-ICU documentations were recorded during dexmedetomidine to clonidine transition, 8 h prior to and 24 h after initial clonidine administration.

Initiation of enteral clonidine to transition off dexmedetomidine is not protocolized or widely employed, and thus, the decision is left to the individual care teams. Lacking a specific protocol for enteral clonidine administration, as a transition from dexmedetomidine, has lead to variations in dosing and dosing frequency.

Major endpoints

The major endpoints evaluated dexmedetomidine discontinuation rates within the first 8 h of clonidine administration and rates of dexmedetomidine re-initiation within 24 h due to clonidine failure. Clonidine has a peak pharmacokinetic effect by 3 h and may provide sedative effects in both normotensive and hypertensive patients, thus an 8h time frame was selected.[25,26]

Minor endpoints

Minor endpoints observed time to dexmedetomidine discontinuation, RASS, and CAM-ICU documentations between patients who discontinued dexmedetomidine within 8 h of clonidine administration (DC), and in patients who did not (nDC). Other minor endpoints observed the rates of rescue sedation use, total clonidine exposure during the first 8 h, initial clonidine doses, and duration and rates of dexmedetomidine infusions prior to clonidine administration.

Safety endpoints

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 $p \leqslant 0.05$. 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.

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/m^2	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.

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 dexmedetomide 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 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.

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 dexmedetomidine rates in the DC group were 0 µg/kg/h (IQR = 0–0.25) and for the nDC group were 0.7 µg/kg/h (IQR = 0.45–0.7) (p = 0.005).

Safety endpoints

Although there were no statistical differences in safety endpoints, hypotension was observed in 6 (35.5%) and 4 (44.4%) in the DC and nDC groups, respectively. Unintentional use of clonidine beyond ICU and hospital discharge was observed in 14 of 26 (54%) and 6 of 26 (23%) patients, respectively.

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

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 ⩽ 0.4 µg/kg/h, n (%)	15 (88.2)	2 (22.2)	0.0016
DEX rate at CLON initiation, µg/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 8 h of clonidine administration; nDC: patients who did not discontinue dexmedetomidine within 8 h 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.

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%, $p \leqslant 0.001$).[32] 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.[25,32,33] 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.,[34] 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.[19]

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.[35] 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.[22] 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

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 documentations were recorded; however, adjudication of appropriate sedation and delirium assessment was not evaluated 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.

References

1. Woods JC, Mion LC, Connor JT, et al. Severe agitation among ventilated medical intensive care unit patients: frequency, characteristics and outcomes. *Intens Care Med* 2004; 30(6): 1066–1072.
2. Jaber S, Chanques G, Altairac C, et al. A prospective study of agitation in a medical-surgical ICU: incidence, risk factors, and outcomes. *Chest* 2005; 128(4): 2749–2757.
3. Skrobik Y, Ahern S, Leblanc M, et al. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. *Anesth Analg* 2010; 111(2): 451–463.
4. Strom T, Stylsvig M and Toft P. Long-term psychological effects of a no-sedation protocol in critically ill patients. *Crit Care* 2011; 15(6): R293.
5. Mansouri P, Javadpour S, Zand F, et al. Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: a randomized clinical trial. *J Crit Care* 2013; 28(6): 918–922.
6. Czerwonka AI, Herridge MS, Chan L, et al. Changing support needs of survivors of complex critical illness and their family caregivers across the care continuum: a qualitative pilot study of towards RECOVER. *J Crit Care* 2015; 30(2): 242–249.
7. Karnatovskaia LV, Johnson MM, Benzo RP, et al. The spectrum of psychocognitive morbidity in the critically ill: a review of the literature and call for improvement. *J Crit Care* 2015; 30(1): 130–137.
8. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41(1): 263–306.
9. Lonardo NW, Mone MC, Nirula R, et al. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. *Am J Respir Crit Care Med* 2014; 189(11): 1383–1394.
10. Hall RI, Sandham D, Cardinal P, et al. Clinical investigations in critical care. Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. *Chest* 2001; 119: 1151–1159.
11. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; 34(5): 1326–1332.
12. Ely EW. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; 291(14): 1753–1762.
13. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; 41(9 Suppl. 1): S30–S38.
14. Strøm T and Martinussen TTP. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; 375(9713): 475–480.
15. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27(12): 2609–2615.
16. Garratt C and Bratty JR. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation. *JAMA* 2012; 307(11): 1151–1160.
17. Knaus AE, Muthig V, Schickinger S, et al. α2-Adrenoceptor subtypes-unexpected functions for receptors and ligands derived from gene-targeted mouse models. *Neurochem Int* 2007; 51(5): 277–281.
18. Abuhasna S, Al Jundi A, Abdelatty W, et al. Evaluation of long-term infusion of dexmedetomidine in critically ill patients: a retrospective analysis. *Int J Crit Illn Inj Sci* 2012; 2(2): 70–74.
19. MacLaren R, Krisl JC, Cochrane RE, et al. A case-based approach to the practical application of dexmedetomidine in critically ill adults. *Pharmacotherapy* 2013; 33(2): 165–186.
20. Ozaki M, Takeda J, Tanaka K, et al. Safety and efficacy of dexmedetomidine for long-term sedation in critically ill patients. *J Anesth* 2014; 28(1): 38–50.
21. Blum RM, Stevens CA, Carter DM, et al. Implementation of a dexmedetomidine stewardship program at a tertiary academic medical center. *Ann Pharmacother* 2013; 47(11): 1400–1405.
22. Gagnon DJ, Riker RR, Glisic EK, et al. Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study. *Pharmacotherapy* 2015; 35(3): 251–259.

23. Reardon DP, Anger KE, Adams CD, et al. Role of dexmedetomidine in adults in the intensive care unit: an update. *Am J Heal Syst Pharm* 2013; 70(9): 767–777.
24. Venn RM, Hell J and Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; 4(5): 302–308. Available at: http://www.ccforum.com/content/pdf/cc712.pdf
25. Wing LMH, Reid JL, Davies DS, et al. Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. *Eur J Clin Pharmacol* 1977; 12(6): 463–469.
26. Klein RH, Alvarez-Jimenez R, Sukhai RN, et al. Pharmacokinetics and pharmacodynamics of orally administered clonidine: a model-based approach. *Horm Res Paediatr* 2013; 79(5): 300–309.
27. Arenas-Lopez S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intens Care Med* 2004; 30(8): 1625–1629.
28. Liatsi D, Tsapas B, Pampori S, et al. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. *Intens Care Med* 2009; 35(2): 275–281.
29. Mariappan R, Ashokkumar H and Kuppuswamy B. Comparing the effects of oral clonidine premedication with intraoperative dexmedetomidine infusion on anesthetic requirement and recovery from anesthesia in patients undergoing major spine surgery. *J Neurosurg Anesth* 2014; 26(3): 192–197.
30. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *Interact Cardiovasc Thorac Surg* 2010; 10(1): 58–62.
31. Farasatinasab M, Kouchek M, Sistanizad M, et al. A randomized placebo-controlled trial of clonidine impact on sedation of mechanically ventilated ICU patients. *Iran J Pharm Res* 2015; 14: 167–175.
32. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370(16): 1504–1513.
33. Robertson D, Goldberg MR, Hollister AS, et al. Clonidine raises blood pressure in severe idiopathic orthostatic hypotension. *Am J Med* 1983; 74(2): 193–200.
34. Srivastava U, Sarkar ME, Kumar A, et al. Comparison of clonidine and dexmedetomidine for short-term sedation of intensive care unit patients. *Indian J Crit Care Med* 2014; 18(7): 431–436.
35. Campbell AJ, Bloomfield R and Noble DW. An observational study of changes to long-term medication after admission to an intensive care unit. *Anaesthesia* 2006; 61(11): 1087–1092.