Predictors of dexmedetomidine-associated hypotension in critically ill patients

Anthony T. Gerlach, Danielle M. Blais, G. Morgan Jones, Pamela K. Burcham, Stanislaw P. Stawicki, Charles H. Cook, Claire V. Murphy

Department of Pharmacy, The Ohio State University Wexner Medical Center, Columbus, OH, 1Department of Clinical Pharmacy, and Neurology and Neurosurgery, Methodist University Hospital, University of Tennessee Health Science Center, Memphis, TN, 2Department of Research and Innovation, St. Luke’s University Health Network, Bethlehem, PA, 3Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Address for correspondence: Dr. Anthony T. Gerlach, Department of Pharmacy, The Ohio State University Wexner Medical Center, Room 368 Doan Hall, 410 West Tenth Avenue, Columbus, OH 43210, USA. E-mail: gerlach.6@osu.edu

ABSTRACT

Background: Dexmedetomidine is commonly used for sedation in the Intensive Care Unit (ICU), and its use may be associated with hypotension. We sought to determine predictors of dexmedetomidine-associated hypotension.

Methods: Retrospective, single-center study of 283 ICU patients in four adults ICUs over a 12 month period. Univariate analyses were performed to determine factors associated with dexmedetomidine-related hypotension. Risk factors significant at the 0.20 level in the univariate analysis were considered for inclusion into a step-wise multiple logistical regression model.

Results: Hypotension occurred in 121 (42.8%) patients with a median mean arterial pressure (MAP) nadir of 54 mmHg. Univariate analyses showed an association between hypotension and age (P = 0.03), Acute Physiology and Chronic Health Evaluation II (APACHE II) score (P = 0.02), baseline MAP (<0.001), admission to the cardiothoracic ICU (P = 0.05), history of coronary artery disease (P = 0.02), and postcardiac surgery (P = 0.0009). Admission to the medical ICU was associated with a decrease in development in hypotension (P = 0.03). There was a trend for hypotension with weight (P = 0.09) and history of congestive heart failure (P = 0.12) Only MAP prior to initiation (odds ratio [OR] 0.97, 95% confidence interval [95% CI] 0.95–0.99; P < 0.0001), APACHE II scores (OR 1.06, 95% CI 1.01–1.12; P = 0.017), and history of coronary artery disease (OR 0.48, 95% CI 0.26–0.90, P = 0.022) were independently associated with hypotension by multivariable analysis.

Conclusions: Dexmedetomidine-associated hypotension is common. Preexisting low blood pressure, history of coronary artery disease, and higher acuity were identified as independent risk factors for dexmedetomidine-associated hypotension.

Key Words: Analgesedation, critically ill, dexmedetomidine, hypotension, sedation

INTRODUCTION

Dexmedetomidine, an α-2 receptor agonist, induces light to moderate sedation without causing respiratory depression and has emerged as an alternative to standard sedation therapy, especially during weaning from mechanical ventilator support.1 Many of the commonly utilized sedative agents in the Intensive Care Unit (ICU), including benzodiazepines and propofol, modulate the gamma-aminobutyric acid system and are known to produce deeper levels of sedation.2,3 These agents have also been associated with a number of adverse effects including systemic accumulation, delirium, and respiratory depression.2,3 Large, randomized trials

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Comparing dexmedetomidine to benzodiazepines has associated dexmedetomidine with increased number of days alive without coma and a larger percentage of time spent at goal sedation. Based on these characteristics, dexmedetomidine use has been increasing in the critical care setting, and this trend has been further augmented by recurring propofol shortages.

Despite the potential clinical benefits, dexmedetomidine is associated with alterations in hemodynamic stability. By agonizing presynaptic α2a receptors, dexmedetomidine produces sedation by decreasing plasma norepinephrine concentrations and may result in clinically significant bradycardia and hypotension. At present, the Food and Drug Administration-approved labeling of dexmedetomidine includes a 1 mcg/kg loading dose given over 10 min followed by continuous infusion of 0.2–0.7 mcg/kg/h. Due to concerns of hypotension and bradycardia, many clinicians choose to omit the loading dose. The maximum recommended rate of infusion for dexmedetomidine also remains controversial. While earlier studies limited infusion rates to those recommended in the package labeling, recent reports have utilized the maximum rates between 1.4 and 4.0 mcg/kg/h, with dosing most frequently limited to 1.5 mcg/kg/h. Although numerous studies have used this dosing strategy, it remains unclear if dosages > 0.7 mcg/kg/h are associated with an increased rate of hypotension. The purpose of this study is to determine the predictors of dexmedetomidine-associated hypotension in critically ill patients.

**METHODS**

**Study design**

A retrospective review of all adult critically ill patients at our academic medical center who received dexmedetomidine from July 16, 2009, to July 15, 2010, was performed. This study included patients treated in any of the following adult critical care areas: (a) Medical ICU, (b) surgical/trauma ICU, (c) bone marrow transplant unit, and (d) cardiothoracic surgery ICU. Dexmedetomidine has been used in our critical care units since April 2001, and our clinical dosing protocol has been described previously. The most recent update to our dexmedetomidine dosing guideline, which included an increase in maximum recommended infusion rate of 1.4 mcg/kg/h was implemented in July of 2009. The Institutional Review Board approval was obtained from the University Office of Responsible Research Practices Institutional Review Board and was carried out with the ethical standards set forth in the Helsinki Declaration on 1975.

ICU patients who received dexmedetomidine were identified through our institutional information warehouse. Patients who were <18 or >89 years of age, incarcerated, pregnant, hypotensive with a baseline mean arterial pressure (MAP) <65 mmHg, and who received dexmedetomidine in the operating theater or for conscious sedation were excluded. Data collected included demographics, medical history, surgical history, indication for hospital and ICU admission, blood pressure, heart rate, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, use of end-organ support (i.e., renal replacement and ventilatory support), dexmedetomidine dosing, and concurrent medications that could contribute to hypotension or treat hypotension (i.e., antihypertensives, vasopressors, inotropes, and continuous intravenous sedation sedatives and analgesics).

**Endpoints and statistical analysis**

The primary endpoint was the development of hypotension defined as MAP <60 mmHg while receiving dexmedetomidine. Secondary endpoints included the duration of mechanical ventilation, ICU and hospital length of stay, mortality, rate of bradycardia, and treatment of hypotension. Bradycardia was defined as heart rate <50 beats/min. Continuous parametric data are presented as a mean (± standard deviation) and analyzed using Student’s t-test. Continuous nonparametric data are presented as median (25–75% interquartile range) and were analyzed using Mann–Whitney U-test. Nominal data are presented as frequency and percentages and were analyzed using the Fisher’s exact test or Chi-square test as appropriate. Following univariate analyses of patients with and without hypotension, multivariable logistic regression was conducted to determine factors independently associated with hypotension. Risk factors significant at the P < 0.20 level in the univariate analysis were considered for inclusion into a step-wise backward multiple logistical regression model. Results are reported as adjusted odds ratio with corresponding 95% confidence intervals. Two-tailed statistical tests were utilized, with significance level set at P < 0.05. All data were analyzed using PASW 19 Software for Windows (SPSS for windows version 19, IBM, Armonk, NY, USA).

**RESULTS**

A total of 283 patients were evaluated, with 45.6% treated in the medical ICU, 36.4% in the surgical/trauma ICU, 16.3% in the cardiothoracic surgery ICU, and 1.7% in the bone marrow transplant unit [Table 1]. The use of concomitant continuous sedative and analgesic infusions was similar between study subgroups, with fentanyl and midazolam being the most commonly administered. Hypotension developed in 42.8% (121) of patients to a median nadir MAP of 54 (50–57) mmHg, and a median time to first hypotensive episode of 5 (2.7–13.4) h. For those who developed hypotension, the median percentage decrease in MAP from baseline...
Patients who experienced dexmedetomidine-associated hypotension were older (55.1 ± 15.2 vs. 50.9 ± 15.6 years; \( P = 0.03 \)) and had a higher APACHE II score on day of dexmedetomidine initiation (22 [18–25] vs. 20 [16–22]; \( P = 0.02 \)). Medical ICU patients were less likely to develop hypotension (38.0% vs. 51.2%; \( P = 0.03 \)) and there was a trend toward more hypotension in those treated in the cardiothoracic ICU (21.5% vs. 12.3%; \( P = 0.05 \)). With regard to past medical and surgical history, there were several significant differences observed in those who experienced hypotension. Patients who developed hypotension were more likely to have a documented history of coronary artery disease (32.2% vs. 16.0%; \( P = 0.009 \)) and underwent cardiac surgery during this admission (18.2% vs. 4.2%; \( P = 0.009 \)).

Patients who developed hypotension during dexmedetomidine administration had lower MAP at the time of dexmedetomidine initiation (82 [70–90] mmHg vs. 90 [78–100] mmHg; \( P < 0.001 \)). Furthermore, more patients in the hypotensive group had a MAP < 70 mmHg at initiation of dexmedetomidine (25.6% vs. 7.4%; \( P < 0.001 \)) [Table 1]. None of the patients received a loading dose and there was no difference in the median maximum dosage of dexmedetomidine between those who developed hypotension and those who did not (0.8 [0.4–1.4] mcg/kg/h vs. 0.7 [0.4–1.0] mcg/kg/h, \( P = 0.34 \)) [Table 2]. Approximately, half of all patients received a maximum dosage > 0.7 mcg/kg/h with one-third ≥ 1 mcg/kg/h, and there were no differences between groups. Although our dexmedetomidine

### Table 1: Demographics

| Characteristic                   | No hypotension (\( n = 162 \)) | Hypotension (\( n = 121 \)) | \( P \)  |
|----------------------------------|---------------------------------|-----------------------------|---------|
| Age (years)\( ^{a} \)            | 50.9 ± 15.6                     | 55.1 ± 15.2                 | 0.027   |
| Female, \( n \) (%)              | 49 (30.2)                       | 37 (30.5)                   | >0.89   |
| Admission weight (kg)            | 89.3 (75.6–107)                 | 82 (68–98)                  | 0.082   |
| APACHE II score                  | 20 (16–22)                      | 22 (18–25)                  | 0.024   |
| Past medical history, \( n \) (%)|                                 |                             |         |
| Atrial fibrillation              | 17 (10.5)                       | 16 (13.2)                   | 0.58    |
| Chronic hypertension             | 47 (29)                         | 27 (22.3)                   | 0.27    |
| Congestive heart failure         | 13 (8)                          | 17 (14)                     | 0.12    |
| Coronary artery disease          | 26 (16)                         | 39 (32.2)                   | 0.02    |
| Diabetes mellitus                | 27 (16.7)                       | 17 (14)                     | >0.99   |
| Heart surgery                    | 12 (7.4)                        | 22 (18.2)                   | 0.009   |
| Liver disease                    | 15 (9.3)                        | 9 (7.4)                     | 0.67    |
| Renal disease                    | 28 (17.3)                       | 23 (19)                     | 0.76    |
| Treatment location, \( n \) (%)  |                                 |                             |         |
| Medical ICU                      | 83 (51.2)                       | 46 (38)                     | 0.03    |
| Surgical/trauma ICU              | 58 (35.8)                       | 45 (37.2)                   | 0.91    |
| Cardiothoracic surgery ICU       | 20 (12.3)                       | 26 (21.5)                   | 0.05    |
| Bone marrow transplant unit      | 1 (0.7)                         | 4 (3.3)                     | 0.37    |
| Baseline MAP (mmHg)              | 90 (78–100)                     | 82 (70–90)                  | <0.001  |
| MAP < 70 mmHg at initiation, \( n \) (%) | 12 (7.4)                          | 31 (25.6)                  | <0.001  |

Data are presented as median (25–75% IQR) unless otherwise noted. \( ^{a} \)Data are presented as mean ± SD. APACHE II: Acute Physiology and Chronic Health Evaluation II, ICU: Intensive Care Unit, MAP: Mean arterial pressure, IQR: Interquartile range, SD: Standard deviation.
There was also no difference in the overall concurrent use of antihypertensive agents between those who experienced hypotension and those who did not (54.5% vs. 45.7%; \( P = 0.15 \)) [Table 3]. Unlike concomitant antihypertensive use, more patients with hypotension were on at least one vasopressor prior to starting dexmedetomidine (14.0% vs. 2.5%; \( P < 0.001 \)). The use of norepinephrine (9.1% vs. 1.8%; \( P = 0.01 \)) and epinephrine (7.4% vs. 1.2%; \( P = 0.01 \)) were more common in the hypotensive group.

### Multivariable analysis

Factors entered into the multivariable analysis were ICU type, history of congestive heart failure, recipient of cardiac surgery during this admission, history coronary artery disease, weight, baseline MAP, and APACHE II score. The multivariable logistic regression analysis identified decreasing baseline MAP, increasing APACHE II score and coronary artery disease as factors independently associated with dexmedetomidine-associated hypotension [Table 4]. For every 1 mmHg decrease in baseline MAP, the odds of dexmedetomidine-associated hypotension increased by 3%. With regards to APACHE II score, each one-unit increase in the severity of illness increased the odds of experiencing a hypotensive episode while on dexmedetomidine by 6%.

### DISCUSSION

Dexmedetomidine-associated hypotension was common in this study with preexisting low blood pressure, history of coronary artery disease, and greater severity of illness identified as independent risk factors. The use of dexmedetomidine in the ICU more than tripled from 2001 to 2007.\(^5\) Since then, numerous shortages of sedative medications (e.g., propofol and benzodiazepines) and the updated 2013 sedation guidelines have further increased the use of dexmedetomidine in the United States.\(^6\) While dexmedetomidine may be an attractive sedative agent due to its lack of respiratory depression and improved protocol discourages titration sooner than every 30 min, titrations quicker than 30 min occurred in 15.4% who developed hypotension and 19.8% who did not (\( P = 0.32 \)).

[Table 2: Dexmedetomidine dosing](#)

| Characteristic | No hypotension (n = 162) | Hypotension (n = 121) | \( P \) |
|---------------|--------------------------|-----------------------|---------|
| Time to initiate dexmedetomidine from ICU admission (h) | 93 (61.5-147.5) | 114 (61.5-180) | 0.67 |
| Maximum dose (mcg/kg/h) | 0.7 (0.4-1.0) | 0.8 (0.4-1.4) | 0.34 |
| Patients with dose > 0.7 mcg/kg/h, n (%) | 78 (48.1) | 66 (54.5) | 0.45 |
| Patients with dose > 1 mcg/kg/h, n (%) | 50 (30.9) | 46 (38) | 0.29 |
| Length of infusion (h) | 27 (12.9-53.5) | 37.5 (13-75) | 0.18 |
| Patients with dose change < 30 minutes, n (%) | 25 (15.4) | 24 (19.8) | 0.32 |
| Number of dexmedetomidine dose changes | 6 (2-11) | 9 (4-14) | 0.003 |

[Table 3: Concurrent medications at dexmedetomidine initiation](#)

| Medication | No hypotension (n = 162) | Hypotension (n = 121) | \( P \) |
|------------|--------------------------|-----------------------|---------|
| At least one vasopressor, n (%) | 4 (2.5) | 17 (14.0) | <0.001 |
| Norepinephrine | 3 (1.1) | 11 (9.1) | 0.01 |
| Epinephrine | 2 (12.3) | 9 (7.4) | 0.011 |
| Dopamine | 0 | 2 (1.7) | 0.18 |
| Vasopressin | 0 | 2 (1.7) | 0.18 |
| At least one inotrope, n (%) | 4 (2.5) | 6 (5.0) | 0.38 |
| Dobutamine | 3 (1.9) | 4 (3.3) | 0.47 |
| Milrinone | 2 (1.2) | 2 (1.7) | >0.99 |
| At least one antihypertensive, n (%) | 74 (45.7) | 66 (54.5) | 0.15 |
| Clonidine | 10 (6.2) | 6 (5.0) | 0.8 |
| Nondihydropyridine CCB | 9 (5.6) | 3 (2.5) | 0.25 |
| Dihydropyridine CCB | 12 (7.4) | 11 (9.1) | 0.66 |
| Beta-blocker | 47 (29.0) | 40 (33.1) | 0.52 |
| ACE-I/ARB | 14 (8.6) | 11 (9.1) | 0.83 |
| Diuretic | 30 (18.5) | 17 (14.0) | 0.34 |
| Nitrate/nitroglycerin | 8 (4.9) | 10 (8.3) | 0.33 |
| Nitropusside | 2 (1.2) | 5 (4.1) | 0.14 |
| Alpha-blocker/hydralazine | 5 (3.1) | 4 (3.3) | >0.99 |

ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CCB: Calcium channel blocker

[Table 4: Multivariable analysis for independent predictors of hypotension](#)

| Variable | Adjusted OR | 95% CI | \( P \) |
|----------|-------------|--------|---------|
| Coronary artery disease | 0.48 | 0.26-0.90 | 0.022 |
| Mean arterial pressure | 0.97 | 0.95-0.99 | 0.001 |
| APACHE II | 1.06 | 1.01-1.12 | 0.017 |

Admission to medical ICU, admission to cardiothoracic surgery ICU, history of congestive heart failure, history of cardiac surgery, and weight were included in the model and did not predict hypotension. ROC AUC 0.70 (95% CI 0.64-0.77); Hosmer-Lemeshow goodness-of-fit test \( P = 0.79 \). APACHE II: Acute Physiology and Chronic Health Evaluation II, CI: Confidence interval, OR: Odds ratio, ICU: Intensive Care Unit, ROC: Receiver operator characteristic, AUC: Area under the curve
delirium profile, it has been associated with hypotension that has ranged from 13% to 98% in clinical studies. We urge caution when initiating dexmedetomidine in patients with low blood pressure or are at the risk of hypotension, especially in those that are undergoing fluid resuscitation.

Hypotension is independently associated with mortality in ICU patients and preventing hypotension may be beneficial to improve outcomes. In the current study, patients who experienced dexmedetomidine-associated hypotension had a higher mortality rate than those who did not. Dexmedetomidine is specific for the α-2a receptor, especially at lower concentrations, resulting in both vasodilation and a blunting of the sympathetic response. Due to these mechanistic considerations, patients are dependent upon adrenergic tone to maintain blood pressure. This is especially true in those who are receiving dexmedetomidine in the settings of hypovolemia, traumatic spinal cord injury, or general anesthetic administration. The use of dexmedetomidine in these patient populations may explain the high rate of hypotension (98%) reported in a recent study in trauma patients where almost 50% of patients had a spinal cord injury. Patients with congestive heart failure or coronary artery disease may also be at risk for dexmedetomidine-induced hypotension due to the blunting of adrenergic tone. Similarly, blood loss and fluid shifts following surgery may place surgical patients at higher risk for hypovolemia, which may explain some of the observed hypotensive events. The observed hypotension may also be another marker of severity of illness. In our study, patients with increased severity of illness and lower baseline MAP were also at increased risk for the development of hypotension during dexmedetomidine administration. Development of a protocol for selective use of dexmedetomidine in these patients may help to reduce the incidence of dexmedetomidine-associated hypotension and potentially mitigate the poor outcomes observed in this population.

Despite concerns that larger doses of dexmedetomidine may be associated with complications, we observed no significant relationship between the development of hypotension and the administration of dexmedetomidine dosages of >0.7 mcg/kg/h. As previously described, dexmedetomidine may produce vasodilatory effects at lower concentrations due to its increased affinity for α-2a receptors. As the concentration increases, dexmedetomidine loses its selectivity and also agonizes α-2b receptors that cause vasoconstriction. Previous pharmacokinetic data in healthy men found that plasma concentrations of dexmedetomidine between 0.7 and 1.2 ng/mL resulted in decreased MAP from baseline and concentrations above 1.9 ng/mL resulted in a return of MAP to baseline. Higher serum concentrations resulted in hypertension. A study of critically ill patients receiving dexmedetomidine infusions as high as 0.7 mcg/kg/h observed serum concentrations ranging from 0.71–1.7 ng/mL. Another study of doses as high as 2.5 mcg/kg/h demonstrated a linear increase in serum concentration of dexmedetomidine (range: 1–6.8 ng/mL) as the infusion rate was increased. Consequently, it is not surprising that increasing dosages above 0.7 mcg/kg/h is not associated with a higher risk of hypotension as it is likely these doses would result in serum concentrations > 1.9 ng/mL. In addition to pharmacokinetic data, recent clinical trials have produced results that suggest similar findings. The dexmedetomidine versus midazolam for continuous sedation in the ICU (MIDEX) and dexmedetomidine versus propofol for continuous sedation in the ICU (PRODEX) studies used infusion rates between 0.2 and 1.4 mcg/kg/h when comparing dexmedetomidine to midazolam or propofol, respectively. The median dexmedetomidine dosage was 0.45 (0.27–0.76) mcg/kg/h in MIDEX and 0.925 (0.67–1.2) mcg/kg/h in PRODEX. Hypotension was more common in the MIDEX study (20.6% vs. 13%; P = 0.03) where the median dosage of dexmedetomidine was <0.7 mcg/kg/h.

Our study has a number of strengths and limitations. Strengths include a relatively large sample size, inclusion in our analyses of several confounding factors for the development of hypotension, including concurrent antihypertensives, which have been poorly described to date. Finally, a large percentage of patients in our study received the treatment with higher doses of dexmedetomidine, allowing evaluation of higher dosing on hypotension. Limitations mainly arise from the retrospective design. We were unable to determine retrospectively the volume status in our cohort of patients which could influence the risk of hypotension. Changes in mechanical ventilator settings that could impact hemodynamic parameters, such as an increase in positive end-expiratory pressure, were not evaluated. Further, 17.3% of patients did have the dose of dexmedetomidine increased too quickly, which may have contributed to the overall high rates of hypotension observed. Finally, our center uses a dexmedetomidine dosing protocol and our results may not be applicable elsewhere.

CONCLUSIONS

Dexmedetomidine-associated hypotension was common and occurred in over 40% of patients. The current analysis identified a baseline MAP < 70 mmHg, history of coronary artery disease, and increasing APACHE II score as factors independently associated with the development of hypotension. High-dose dexmedetomidine was not significantly associated with increased risk of hypotension. Clinicians should use dexmedetomidine cautiously in patients with low baseline blood pressure...
and increasing the severity of illness. Further trials are needed to determine factors associated with the development of hypotension and potential impact of protocols on minimizing the risk of this adverse effect.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. Ann Pharmacother 2009;43:2064-74.
2. Barr J, Fraser GL, Puntillo K, Ely EW, Dellas G, Dasta JF, 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;41:263-306.
3. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med 2009;37:3031-9.
4. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. JAMA 2007;298:2644-53.
5. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. JAMA 2009;301:489-99.
6. Gerlach AT, Murphy CV. Sedation with dexmedetomidine in the intensive care setting. Open Access Emerg Med 2011;3:77-85.
7. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
8. Mistraletti G, Cerri B. Analgesia and sedation in high-risk critically ill patients: Still waiting for evidence about remifentanil. Minerva Anestesiol 2012;78:7-9.
9. Devabhaktuni S, Pajoumand M, Williams C, Kufra JA, Watson K, Stein DM. Evaluation of dexmedetomidine: Safety and clinical outcomes in critically ill trauma patients. J Trauma 2011;71:1164-71.