NCPD 1.5 ANCC Contact Hours

Evaluating the Effect of a Dosing and Titration Protocol on Dexmedetomidine-Induced Hypotension in Trauma Patients

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BACKGROUND: Dexmedetomidine is an α-2 receptor agonist commonly used as a continuous infusion for sedation and analgesia; however, dose-dependent hypotension may limit its utility. Despite its widespread use, there is no consensus on appropriate dosing and titration.

OBJECTIVE: The objective of this study was to determine whether a dexmedetomidine dosing and titration protocol is associated with decreased rates of hypotension in trauma patients.

METHODS: This pre-post intervention study took place at a Level II trauma center in the Southeastern United States from August 2021 to March 2022 and included patients admitted by the trauma service to either the surgical trauma intensive care unit or intermediate care unit and received dexmedetomidine for greater than or equal to 6 hours. Patients were excluded if they were hypotensive or on vasopressors at baseline. The primary outcome was incidence of hypotension. Secondary outcomes included dosing and titration practices, initiation of a vasopressor, incidence of bradycardia, and time to goal Richmond Agitation Sedation Scale (RASS) score.

RESULTS: Fifty-nine patients met inclusion criteria: 30 in the pre-intervention group and 29 in the post-intervention group. Protocol adherence in the post group was 34% with a median of one violation per patient. Rates of hypotension were similar between the groups (60% vs. 45%, $p = .243$) but significantly lower in the post group patients with zero protocol violations (60% vs. 20%, $p = .029$). The post group also had a significantly lower maximal dose (1.1 vs. 0.7 μg/kg/hr, $p < .001$). There were no significant differences in the initiation of a vasopressor, incidence of bradycardia, or time to goal RASS.

CONCLUSION: Adherence to a dexmedetomidine dosing and titration protocol significantly decreased incidence of hypotension and maximal dexmedetomidine dose without increasing time to goal RASS score in critically ill trauma patients.

KEY WORDS: Critical care, Dexmedetomidine, Hypotension, Sedation, Trauma

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Dexmedetomidine is an α-2 receptor agonist commonly used as a continuous infusion for sedation and analgesia in the intensive care unit. Because of its unique mechanism, dexmedetomidine does not depress the respiratory drive, making it an attractive agent in non-intubated patients or those being weaned from mechanical ventilation. In addition, its analgesic effects can be especially helpful in trauma patients and has been shown to decrease opioid requirements (Kaye et al., 2020). However, α-2 agonism resulting in vasodilation can lead to significant hypotension in up to 25% of patients treated with dexmedetomidine (Hospira Inc., 2013), which may limit its utility.

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Peyton M. Kurtz, Jason VanLandingham, and Leslie Roebuck had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Peyton Kurtz was involved in conceiving and designing the work, analyzing and interpreting the data, collecting data or other material, writing the manuscript or part of the manuscript, and approving the final version of the manuscript. Jason VanLandingham was involved in conceiving and designing the work, analyzing and interpreting the data, revising the manuscript to make important changes in content, and approving the final version of the manuscript. Michael Cormican was involved in conceiving and designing the work, revising the manuscript to make important changes in content, and approving the final version of the manuscript. Kyle Gibson was involved in conceiving and designing the work, revising the manuscript to make important changes in content, and approving the final version of the manuscript. Leslie Roebuck was involved in conceiving and designing the work, analyzing and interpreting the data, revising the manuscript to make important changes in content, and approving the final version of the manuscript.

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KEY POINTS

- There is no established standard or guideline for dosing and titration of dexmedetomidine.
- Because dexmedetomidine is an α-2 receptor agonist, hypotension is a common side effect that limits its utility and often leads to discontinuation.
- Implementing a standardized dosing and titration protocol for dexmedetomidine may increase its clinical utility by decreasing rates of hypotension in trauma patients.

Despite its widespread use, there is no consensus on appropriate dosing and titration of dexmedetomidine and practices vary greatly. Product labeling recommends a 1 μg/kg loading dose administered over 10 minutes, followed by a maintenance infusion of 0.2–0.7 μg/kg/hr for no more than 24 hr (Hospira Inc., 2013). However, loading doses have generally become undesirable after several studies showed that they are associated with increased rates of bradycardia and hypotension (Ickeringill et al., 2004; Venn et al., 1999), as well as possible transient hypertension due to stimulation of peripheral α-receptors (Hospira Inc., 2013). Further research has shown that doses of up to 1.5 μg/kg/hr for durations greater than 24 hr are generally safe and well tolerated (Jones et al., 2011). Conversely, studies have suggested that doses greater than 0.7 μg/kg/hr confer no additional sedative benefit and are associated with increased incidence of hypotension (Devabhakthuni et al., 2011; Gerlach et al., 2016). Gerlach et al. (2009) is the only previous study that described specific dosing and titration parameters and found that rates of hypotension were significantly reduced with set starting doses and titration frequencies. Our institution had no standard protocols in place, and there were subjective reports of widespread hypotension among our trauma population.

OBJECTIVE

The objective of this study was to determine whether implementation of a formal dexmedetomidine dosing and titration protocol is associated with decreased rates of hypotension in trauma patients.

METHODS

Study Design

This retrospective pre-post intervention study was conducted at a large community teaching hospital and Level II trauma center in Georgia, United States. Patients were included if they were at least 18 years of age, admitted to the surgical trauma intensive care unit or trauma intermediate care unit by a trauma acute care surgery attending, and received dexmedetomidine for greater than or equal to 6 hours. Patients were excluded if they were hypotensive (mean arterial pressure [MAP] <65 mmHg) at the time of dexmedetomidine initiation, if they were on a vasopressor prior to dexmedetomidine initiation, or if they were pregnant or incarcerated. Eligible patients were identified via the electronic medical record. Pre-intervention data collection took place from August to October 2021, the intervention was implemented in November 2021, and post-intervention data collection took place from January to March 2022. The study design was deemed exempt by the WCG institutional review board (institutional review board # 1-1484168-1). The SQUIRE 2.0 guideline (Ogrinc et al., 2016) was used to ensure proper reporting of the methods, results, and discussion.

Intervention

The intervention consisted of implementing a standardized dexmedetomidine dosing and titration protocol (Table 1). Providers and nursing staff were educated on the protocol via in-services and email communications. The protocol was also displayed on the medication administration record in the electronic medical record. The protocol was loosely adapted from a previously published protocol by Gerlach et al. (2009) that was shown to significantly reduce hypotension in critically ill surgical patients.

Data Collection

Data were collected retrospectively via the electronic medical record (Epic). Baseline data collected included demographics, height and weight, use of mechanical ventilation, hospital unit, selected past medical history, and utilization of an additional sedative or analgesic infusion. The Sequential Organ Failure Assessment (SOFA) score is a validated tool to assess the degree of organ dysfunction and risk of mortality in critical illness (Lambden et al., 2019) and was calculated based on values collected on the day of dexmedetomidine initiation. Dexmedetomidine dosing and titration practices were

Table 1. Dexmedetomidine Dosing and Titration Protocol

RASS Score	Starting Dose
≤ +1	0.2 μg/kg/hr
+2	0.4 μg/kg/hr
+3 or +4	0.6 μg/kg/hr
Titrate up by no more than 0.2 μg/kg/hr every 30 min	
Contact physician to request push-dose medication while initiation or dose increase is taking effect	
Titrate down as needed	
Maximum dose of 1.5 μg/kg/hr	

Note. RASS = Richmond Agitation-Sedation Scale.

characterized by collecting total infusion duration and initial and maximal doses, time to maximal dose, frequency of titrations, and change in dose of titrations during the first 24 hours of the dexmedetomidine infusion as documented by nursing staff in the electronic medical record. Heart rate, blood pressure, initiation of a vasopressor, and Richmond Agitation Sedation Scale (RASS) scores were also collected for the first 24 hours after the start of a dexmedetomidine infusion. The RASS score is a validated method to assess levels of agitation or sedation in the intensive care unit (Ely et al., 2003). Hospital and intensive care unit length of stay were recorded.

Outcomes

The primary outcome of the study was the incidence of hypotension, defined as a MAP of less than 65 mmHg. Secondary outcomes included characterization of dexmedetomidine dosing and titration practices, initiation of a vasopressor, incidence of bradycardia (defined as a heart rate of <50 beats per minute), time to goal RASS score, and hospital and intensive care unit length of stay. All outcomes were measured from initiation of dexmedetomidine up to 24 hours or until discontinuation, whichever was sooner. Adherence to protocol was also assessed in the post-intervention group.

Statistical Analysis

Statistical analyses were pre-specified and performed by an independent statistician. Discrete and continuous data were analyzed using χ^2 and Mann–Whitney *U* tests, respectively. *p* values less than .05 were considered significant. Discrete variables are reported as a value and the percentage of the total; continuous variables are reported as a median and interquartile range. To better

Table 2. Baseline Characteristics[a]

Characteristic	Pre-intervention (*n* = 30)	Post-intervention (*n* = 29)	*p*
Hospital unit			.478
Trauma intermediate care	5 (17%)	3 (10%)	
Surgical trauma intensive care	25 (83%)	26 (90%)	
Age (years)	55.5 (36–64)	68 (39–77)	.048
Sex			.926
Male	20 (67%)	19 (66%)	
Female	10 (33%)	10 (34%)	
Race			.512
White	24 (80%)	23 (79%)	
Black or African American	2 (7%)	4 (14%)	
Other or unknown	4 (13%)	2 (7%)	
Ethnicity			.157
Non-Hispanic	28 (93%)	29 (100%)	
Hispanic	2 (7%)	0 (0%)	
Weight (kg)	79.8 (68–97.4)	74.3 (61–90.1)	.317
BMI (kg/m^2)	26.7 (23–33.2)	23.4 (20.9–29.8)	.118
Relevant past medical history			.659
Coronary artery disease	5 (17%)	6 (21%)	
Hypotension	1 (3%)	0 (0%)	
Additional sedative infusion[b]	15 (50%)	7 (24%)	.040
Fentanyl	10 (33%)	1 (3%)	
Propofol	6 (20%)	1 (3%)	
Ketamine	0 (0%)	5 (17%)	
Midazolam	4 (13%)	0 (0%)	
SOFA score	5 (3–7)	4 (2–6)	.202
Mechanical ventilation	20 (67%)	16 (55%)	.366

Note. BMI = body max index; SOFA = Sequential Organ Failure Assessment.

[a]All values are represented as median (interquartile range) or *n* (%).

[b]Some patient received greater than one additional sedative infusion.

assess the effect of the protocol, a pre-specified secondary analysis was conducted in which outcomes were reported in the context of the overall post-intervention group and the post-intervention per protocol group. The latter group was comprised of patients in the post-intervention group that had zero protocol violations.

RESULTS

Overall, 126 patients received dexmedetomidine during the study period. Sixty-seven patients were excluded: 37 were on vasopressors before the initiation of dexmedetomidine, 24 received dexmedetomidine for less than 6 hours, five were not admitted by a trauma acute care surgery attending, and one was pregnant. Fifty-nine patients were included in the study, with a total of 30 patients in the pre-intervention group and 29 patients in the post-intervention group. Baseline characteristics were comparable between the groups, with the exception of age (55.5 vs. 68 years, $p = .048$) and utilization of an additional sedative infusion (50% vs. 24%, $p = .040$; Table 2).

Protocol adherence in the post-intervention group was 34% (Figure 1). There was a median of one protocol violation per patient. Thirty-one percent of patients were started on the incorrect dose, 24% had at least one titration sooner than 30 minutes from initiation or last dose increase, and 52% had at least one titration greater than 0.2 μg/kg/min.

Dexmedetomidine dosing and titration practices are summarized in Table 3. The infusion duration and initial doses were similar between the groups. The maximal dose was significantly higher in the pre-intervention group than in both the post-intervention group (1.1 vs. 0.7 μg/kg/hr, $p < .001$) and the post-intervention per protocol group (1.1 vs. 0.5 μg/kg/hr, $p < .001$). Although the number of titrations was similar between the pre- and post-intervention groups (6.5 vs. 6, $p = .214$), the post-intervention per protocol group had significantly fewer titrations (6.5 vs. 2.5, $p = .003$).

The primary outcome of hypotension occurred in 18 (60%) pre-intervention patients and 13 (45%) post-intervention patients, although the difference was not statistically significant (Table 4). However, the difference was significant when comparing the pre-intervention and post-intervention per protocol groups (60% vs. 20%, $p = .029$). The dose at the time of hypotension was significantly lower in both the post-intervention (0.4 μg/kg/hr) and post-intervention per protocol (0.2 μg/kg/hr) groups than in the pre-intervention group (1 μg/kg/hr). Hypotension requiring the initiation of vasopressor was numerically less common in the post-intervention group than in the pre-intervention group (10% vs. 23%, $p = .184$) and did not occur in the

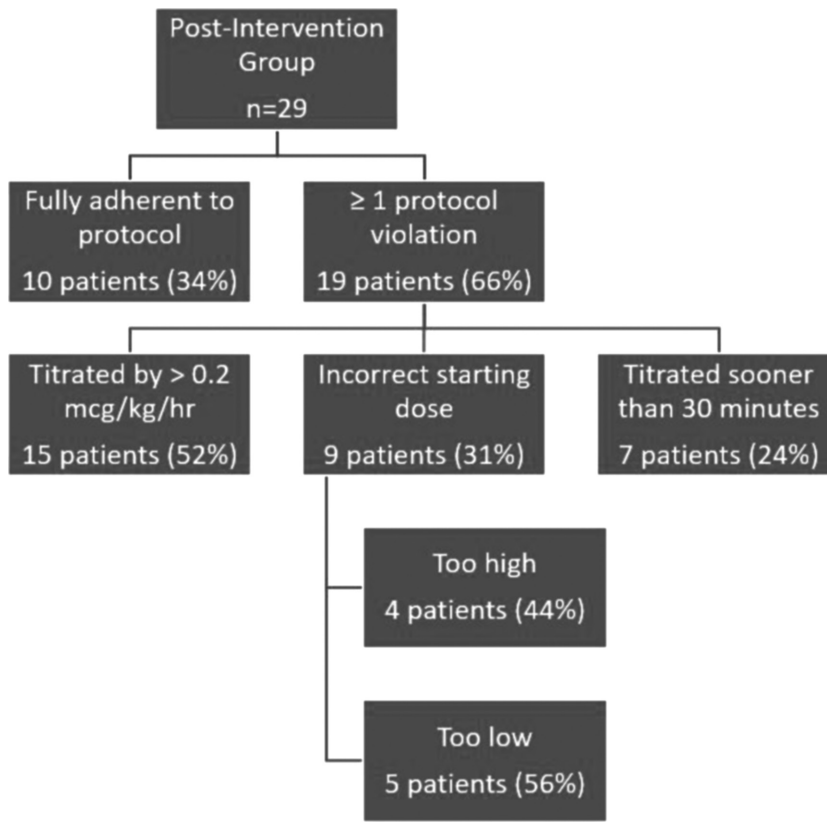

Figure 1. Protocol adherence.

Table 3. Dexmedetomidine Dosing and Titration[a]

Characteristic	Pre-intervention ($n = 30$)	Post-intervention ($n = 29$)	p[b]	Post-intervention per Protocol[c] ($n = 10$)	p[d]
Infusion duration (hours)	30.8 (14.5–71.2)	31.3 (16.5–52.7)	.982	24.8 (10.5–36.6)	.390
Initial dose (μg/kg/hr)	0.2 (0.2–1)	0.2 (0.2–0.4)	.192	0.2 (0.2–0.2)	.139
Maximum dose (μg/kg/hr)	1.1 (1–1.5)	0.7 (0.5–1)	<.001	0.5 (0.2–0.6)	<.001
Time to maximum dose (hours)	1.7 (0.4–8.5)	5.2 (0.13–14.7)	.479	2.28 (0–9.7)	.500
Number of titration	6.5 (5–8)	6 (3–8)	.214	2.5 (0–5)	.003

[a]All values are represented as median (interquartile range) or *n* (%).

[b]Compares pre-intervention and post-intervention groups.

[c]Post-intervention per protocol represents a subset of post-intervention patients with zero protocol violations.

[d]Compares pre-intervention and post-intervention per protocol groups.

post-intervention per protocol group (0% vs. 23%, $p = .093$), but this finding did not reach statistical significance. There were no differences in number of instances of hypotension, time to hypotension, lowest MAP, bradycardia, or length of stay between any of the groups. There was also no difference in time to goal RASS score.

DISCUSSION

These findings suggest that adherence to the dexmedetomidine dosing and titration protocol significantly reduced hypotension in trauma patients without prolonging the time to goal RASS score. More than half of the patients in the pre-intervention group experienced hypotension, which could be due in part to the lack of a standardized protocol leading to rapid titration and high doses along with the innate instability of many trauma patients. In addition, although severity of illness measured via SOFA score and rates of mechanical ventilation were similar between the groups, the pre-intervention group was more likely to be on a concurrent sedative or analgesic infusion that may inherently contribute to hypotension and may also suggest a more critical diagnosis. The 20% rate of hypotension in the post-intervention per protocol group was fairly consistent with the 16% rate in the post-group from the study by Gerlach et al. (2009) from which our protocol was adapted, both of which were lower than the 25% rate cited in the clinical trials (Hospira Inc., 2013).

Although dosing and titration differences between the groups were expected after implementation of the protocol, there were some surprising

Table 4. Outcomes[a]

Characteristic	Pre-intervention ($n = 30$)	Post-intervention ($n = 29$)	p[b]	Post-intervention per Protocol[c] ($n = 10$)	p[d]
Hypotension	18 (60%)	13 (45%)	.243	2 (20%)	.029
Dose at the time of hypotension (μg/kg/hr)	1 (0.55–1)	0.4 (0.2–0.8)	.012	0.2 (0.2–0.2)	.029
Time to hypotension (hours)	1.85 (0.97–11.1)	2.27 (0.78–6.37)	.759	0.78 (0.77–0.78)	.152
Lowest mean arterial pressure (mmHg)	60.5 (57–63)	59 (52.5–60)	.131	57 (55–59)	.375
Hypotension requiring vasopressor	7 (23%)	3 (10%)	.184	0 (0%)	.093
Number of instances of hypotension	1 (0–2)	0 (0–2.5)	.556	0 (0–0)	.111
Bradycardia	6 (20%)	3 (10%)	.303	1 (10%)	.471
Number of instances of bradycardia	0 (0–0)	0 (0–0)	.389	0 (0–0)	.524
Baseline RASS score	1 (−2 to 2)	1 (−1 to 2)	.637	0 (−1 to 1)	.874
Time to goal RASS score (hours)	0 (0–0.75)	0 (0–0.53)	.801	0 (0–0)	.658
Hospital length of stay (days)	13 (6–21)	14 (7–31)	.593	16 (6–26)	.971
Intensive care unit length of stay (days)	5 (2–9)	4 (3–10)	.9211	4 (2–9)	.564

Note. RASS = Richmond Agitation-Sedation Scale.

[a]All values are represented as median (interquartile range) or *n* (%).

[b]Compares pre-intervention and post-intervention.

[c]Post-intervention per protocol represents a subset of post-intervention patients with zero protocol violations.

[d]Compares pre-intervention and post-intervention per protocol groups.

findings. The median initial dose was 0.2 μg/kg/hr across the groups, despite a much higher maximal dose (1.1 μg/kg/hr) in the pre-intervention group. Interestingly, the maximal dose in the post group was 0.7 μg/kg/hr, which is thought to be the point above which additional sedative benefit is not seen (Devabhakthuni et al., 2011; Gerlach et al., 2016). The 30 minute titration period required in the post-intervention group may have allowed for adequate distribution of dexmedetomidine before a subsequent dose increase, ultimately leading to a lower dose and fewer titrations required to achieve the same level of sedation. The dose at the time of hypotension was significantly lower in the post group, which may suggest that there are both dose- and patient-related factors, such as age and use of concurrent sedative infusions, contributing to the development of hypotension in patients receiving dexmedetomidine.

LIMITATIONS

Non-adherence to the protocol was a significant limitation of the study despite in-person provider and nursing in-services, email education, protocol handouts posted on the units, and a preplanned washout period between protocol implementation (November 2021) and data collection (beginning January 2022). Possible explanations for this include difficulty obtaining buy-in for a more restrictive policy and high rates of contract staffing that may have been less familiar with institutional practices at baseline. Despite this limitation, the study showed a numerical decrease in hypotension in a real-world scenario. Additional limitations include the retrospective study design, lack of analysis of potentially confounding baseline characteristics such as liver function and substance use history, relatively small sample size, inability to capture administration of bolus doses of sedatives and analgesics that may also contribute to hypotension, and reliance on nursing documentation of vital signs and dexmedetomidine titration. Although this study expands upon the previously available knowledge on optimal dexmedetomidine dosing and titration, further prospective research is necessary to definitively validate the protocol.

CONCLUSION

Adherence to a dexmedetomidine dosing and titration protocol significantly decreased incidence of hypotension and maximal dexmedetomidine dose without increasing time to goal RASS in critically ill trauma patients.

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