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Original Article

Retrospective Review of Critically Ill Patients Experiencing Alcohol Withdrawal: Dexmedetomidine Versus Propofol and/or Lorazepam Continuous Infusions

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Abstract

Background: Alcohol withdrawal symptoms can be difficult to manage and may lead to an intensive care unit (ICU) admission. Patients experiencing severe alcohol withdrawal often require high doses of sedatives, which can lead to respiratory depression and the need for endotracheal intubation. Dexmedetomidine, an alpha-2 adrenoreceptor agonist, provides adequate sedation with little effect on respiratory function when compared to other sedatives.

Objective: To evaluate sedation with a continuous infusion of dexmedetomidine versus propofol and/or lorazepam in critically ill patients experiencing alcohol withdrawal.

Methods: A retrospective chart review was conducted on ICU admissions between March 2002 and April 2009 for alcohol withdrawal patients who necessitated treatment with a continuous infusion of dexmedetomidine, propofol, and/or lorazepam. Primary outcomes included the incidence of mechanical ventilation, length of mechanical ventilation (if applicable), and ICU and hospital length of stay.

Results: Fifteen patients were treated with a continuous infusion of dexmedetomidine, and 17 were treated with an infusion of propofol and/or lorazepam. Two patients (13.3%) required intubation and mechanical ventilation in the dexmedetomidine group versus 10 (58.8%) in the propofol and/or lorazepam group ($P = .006$). Length of stay in the ICU was 53 hours for patients treated with dexmedetomidine versus 114.9 hours in the propofol and/or lorazepam group ($P = .016$). Hospital length of stay was less for the dexmedetomidine group, 135.8 hours versus 241.1 hours in the propofol and/or lorazepam group ($P = .008$).

Conclusions: Dexmedetomidine use was associated with a decrease in the incidence of endotracheal intubation when used to sedate patients experiencing alcohol withdrawal. Patients transferred to a lower level of care faster and were discharged from the hospital sooner when treated with dexmedetomidine.

Key Words—alcohol, dexmedetomidine, lorazepam, propofol, withdrawal

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There are approximately 18.3 million people in the United States dependent on or abusing alcohol and 2.9 million people requiring treatment for problems related to alcohol use.[1] The impact of alcohol withdrawal syndrome can be devastating, both physically and neurologically. The syndrome can include headache, anxiety, hallucinations, nausea and vomiting, sweating, seizures, irritability, and the most severe form of alcohol withdrawal, delirium tremens. Patients experiencing delirium tremens have a

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mortality rate of up to 5%.[2] The American Society of Addiction Medicine guidelines for the management of alcohol withdrawal delirium recommend sedative-hypnotic drugs, such as benzodiazepines, as the primary agents for managing alcohol withdrawal syndrome.[3]

The goal of alcohol withdrawal treatment is to relieve the patients' agitation and prevent the further development of more severe symptoms. Some patients may experience symptoms such as increased levels of anxiety, hallucinations, and delirium tremens. In these severe cases, escalating benzodiazepine doses (to include initiation of a continuous infusion) or initiation of another sedative, such as propofol or phenobarbital, becomes necessary to control agitation. The use of sedatives can cause a decrease in respiratory drive, which can lead to patients requiring transfer to a higher level of care with the potential for intubation and mechanical ventilator support.

At North Colorado Medical Center (NCMC), patients undergoing alcohol withdrawal are initially treated with benzodiazepines. If escalating doses of benzodiazepines are unable to control agitation and other alcohol withdrawal symptoms, patients are evaluated by the physician for transfer to the intensive care unit (ICU). In the past, the standard of care in the NCMC ICU for patients experiencing severe alcohol withdrawal not controlled by intermittent benzodiazepines was the initiation of a benzodiazepine and/or propofol infusion based on the physician's assessment and preference. Often these patients required intubation and mechanical ventilation. Recently, however, the sedation of patients experiencing severe alcohol withdrawal is increasingly being managed with dexmedetomidine in the ICU at NCMC.

Clonidine has historically been used for treatment and prophylaxis of the symptoms of alcohol withdrawal.[3-9] Dexmedetomidine is a centrally acting, relatively selective, alpha2-adrenergic agonist similar to clonidine with sedative and analgesic properties. Dexmedetomidine reduces the stress response, decreases norepinephrine and epinephrine levels, and attenuates increases in heart rate and blood pressure without depressing the respiratory drive.[10,11]

The use of dexmedetomidine has been noted in multiple case reports, case series, and one small randomized controlled trial as a possibly effective agent for the management of alcohol withdrawal.[12-19] The case reports and case series primarily reported on safety, reduced benzodiazepine doses, and reduced delirium scores in the use of dexmedetomidine in alcohol withdrawal patients. The one randomized, blinded, placebo-controlled trial published to date by Mueller et al compared dexmedetomidine to placebo in patients with severe alcohol withdrawal. The primary endpoint was benzodiazepine requirements in the first 24 hours and cumulative dose over the first 7 days of hospitalization. They reported a reduced 24-hour benzodiazepine dose in the dexmedetomidine group and no difference in the 7-day cumulative dose between groups.[12]

One of the main advantages of dexmedetomidine is that it does not cause respiratory depression.[11] This is especially important in patients admitted to the ICU for severe alcohol withdrawal. Studies have demonstrated that patients admitted to the ICU with severe alcohol withdrawal have a high rate of intubation, reportedly 22% to 65%.[20] Ventilator-associated pneumonia (VAP) can occur in 10% to 20% of patients receiving greater than 48 hours of mechanical ventilation. Patients who contract VAP have increased hospital costs of more than $10,000 per day, increased ICU length of stay by 5 to 7 days, and, in some reports, increased mortality.[21] Furthermore, intubation and mechanical ventilation on ICU day 1 has been recognized as a predictor of a longer length of hospital stay.[22]

Assessment and documentation of the effectiveness of dexmedetomidine for treatment of alcohol withdrawal, while growing rapidly, is still lacking in the medical literature. The purpose of this retrospective observational study was to evaluate the incidence and duration of mechanical ventilation and the length of ICU and hospital stay in alcohol withdrawal patients treated with dexmedetomidine, propofol, and/or lorazepam continuous infusions.

METHODS

The study was a retrospective chart review conducted on admissions between March 2002 and April 2009. Patients were identified based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes for alcohol withdrawal. Each patient had a diagnosis of alcohol withdrawal listed as 1 of the first 5 diagnoses and were treated in the ICU during their admission.

The investigational review board of NCMC approved the protocol before data collection began. Waiver of informed consent and Health Insurance Portability and Accountability Act authorization were granted due to the observational and retrospective nature of the review.

All adult critical care patients were included in the review if they had a diagnosis of alcohol withdrawal and were treated with a continuous infusion of

dexmedetomidine, propofol, or lorazepam. Patients were excluded only if they were treated using a continuous infusion of dexmedetomidine and an infusion of propofol or a continuous infusion of dexmedetomidine and a continuous infusion of lorazepam or the combination of all 3 drugs.

The following data were collected at the time of chart review: incidence of mechanical ventilation, length of mechanical ventilation (if applicable), ICU and hospital length of stay, age, and sex. Additionally, CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol, revised) score on admission to the ICU was recorded, when available, to assess the severity of alcohol withdrawal syndrome symptoms at the time of admission to the ICU. Because CIWA-Ar was not done routinely at NCMC until December 2007, values are missing for 13 patients (2 in the dexmedetomidine group and 11 in the propofol and/or lorazepam group).

The primary outcomes assessed were mechanical ventilation, length of mechanical ventilation (if applicable), ICU length of stay, and hospital length of stay.

Time of intubation was determined from the time of written orders for the patient to be intubated and/or the time of the orders written for rapid sequence intubation (RSI) medications. The time of extubation was determined from written orders to extubate the patient from the critical care physician. Time of admission to the ICU was determined from the date and time of signed orders from the admitting critical care physician. Hospital length of stay was determined from admission and discharge times recorded by the admissions department and recorded in the permanent medical record.

Patients treated with continuous infusion dexmedetomidine versus continuous infusion propofol, lorazepam, or both propofol and lorazepam were compared in terms of age and sex. Continuous variables, when normal, were tested using the *t* test, and when not normal, using the Mann-Whitney test. Categorical data were analyzed using the Fisher's exact test. Linear regression was used to determine significant predictors of length of ICU stay and length of hospital stay, and logistic regression was used to determine use of mechanical ventilation. A *P* value of less than .05 was considered significant.

RESULTS

Between March 2002 and April 2009, 55 patients were admitted to the ICU with one of their first 5 diagnoses listed as alcohol withdrawal. Twenty patients were not included in the analysis because they were not treated with a continuous infusion of dexmedetomidine, propofol, or lorazepam. Two patients were not included in the analysis because they were treated with a combination of lorazepam and dexmedetomidine continuous infusions. One patient was not included due to treatment with a combination of propofol and dexmedetomidine continuous infusions. Thirty-two patients who were treated with a continuous infusion of dexmedetomidine, propofol, or lorazepam, or a combination of propofol and lorazepam, were included in the analysis.

Of the 32 patients analyzed, 15 were treated with a continuous infusion of dexmedetomidine. Seventeen patients were treated using propofol and/or lorazepam.

Analysis revealed that patients who were admitted to the ICU with 1 of their first 5 diagnoses being alcohol withdrawal were similar in gender and age between the dexmedetomidine and the propofol and/or lorazepam groups. There were 3 patients included in the study with "trauma" as 1 of their first 5 diagnoses (2 in the dexmedetomidine group and 1 in the propofol and/or lorazepam group).

Dexmedetomidine-treated patients were found to have higher CIWA-Ar scores than the propofol and/or lorazepam group (23.1 vs 15), when scores were available, at the time of admission to the ICU ($P = .039$).

Patients were less likely to require intubation and mechanical ventilation if they were treated with a dexmedetomidine infusion. Ten patients in the propofol and/or lorazepam group were supported with mechanical ventilation compared to 2 in the dexmedetomidine group requiring mechanical ventilation ($P = .006$). If tracheal intubation was necessary, however, time of mechanical ventilation was 0.95 days (22.8 hours) in the dexmedetomidine group and 4.1 days (97.6 hours) in the propofol and/or lorazepam group ($P = .264$). Length of stay in the ICU was 2.2 days (53 hours) for patients treated with dexmedetomidine versus 4.8 days (114.9 hours) for those treated with propofol and/or lorazepam ($P = .016$). Overall hospital length of stay was also less for the dexmedetomidine-treated group, 5.7 days (135.8 hours) versus 10 days (241.1 hours) in the propofol and/or lorazepam group ($P = .008$). See **Table 1**.

DISCUSSION

Dexmedetomidine decreased the incidence of tracheal intubation when critically ill patients experiencing severe withdrawal were sedated. As mentioned earlier, mechanical ventilation on ICU day 1 has been recognized as a predictor of a longer hospital length of stay and this statement has been reinforced by the results of this study.

Table 1. Primary endpoints and patient parameters in critically ill patients experiencing alcohol withdrawal receiving dexmedetomidine versus propofol and/or lorazepam continuous infusions

Parameter	Patients treated with dexmedetomidine (*n* = 15)	Patients treated with propofol and/or lorazepam continuous infusion (*n* = 17)	*P* value*
Mean age, years	44.8	49	.316
Sex (male), *n*	11	16	.098
Mean CIWA-Ar score[a]	23.1	15	.039
Trauma patient, *n*	2	1	.589
Mechanical ventilation, *n*	2	10	.006
Mean length of intubation[b], days	0.95	4.1	.264
Mean intensive care unit length of stay, days	2.2	4.8	.016
Mean hospital length of stay, days	5.7	10	.008

[a]Thirteen patients (2 in the dexmedetomidine group, 11 in the propofol and /or lorazepam group) did not have Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) scores on admission to the intensive care unit.
[b]Patients treated with dexmedetomidine requiring intubation, *n* = 2; patients treated with propofol and/or a benzodiazepine requiring intubation, *n* = 10.
**P* value of less than .05 was considered significant.

Patients treated with dexmedetomidine were transferred sooner to a lower level of care from the ICU as well as discharged sooner from the hospital when compared to those patients treated with propofol and/or lorazepam infusions.

Dexmedetomidine currently has a much higher acquisition cost than propofol and lorazepam; however, if we observe a reduced length of ICU and hospital stay and a decrease in the rate of mechanical ventilation with the use of dexmedetomidine, an overall cost savings may be appreciated. The patent on dexmedetomidine is due to expire at the end of 2014, so we should see a reduced acquisition cost for dexmedetomidine in the near future.

ICU delirium is associated with increased morbidity, mortality, and longer hospital length of stay.[23-26] The results of several studies have shown that dexmedetomidine can reduce the incidence of delirium in ICU patients when compared to midazolam, lorazepam, or propofol.[27,28] In addition to reducing the need for intubation, reduced delirium with the use of dexmedetomidine may be a contributing factor to decreased ICU length of stay.

When dexmedetomidine was introduced in the United States, it was approved for the first 24 hours of mechanical ventilation in the ICU. Because dexmedetomidine does not cause respiratory depression, it has since received approval for use in nonventilated patients prior to and/or during surgical interventions and other procedures.[18,27,29] A number of studies have demonstrated the safe use of dexmedetomidine for longer than 24 hours and in some cases up to 30 days.[28,30-32] At NCMC, dexmedetomidine is routinely used for longer than 24 hours in the ICU. The manufacturers' recommended dosing range for dexmedetomidine was initially 0.2 to 0.7 mcg/kg/h. The maximum dose has recently been approved up to 1 mcg/kg/h for procedural sedation.[29] Doses up to 1.4 to 1.5 mcg/kg/h have been safely used in studies.[28,30-32] The NCMC ICU sedation protocol allows a maximum of dexmedetomidine infusion rate of 1.5 mcg/kg/h.

The manufacturer recommends initiating dexmedetomidine with a loading dose of 1 mcg/kg over 10 minutes[29]; however, this is not always done at NCMC due to the potential risk of adverse hemodynamic effects. If a loading dose is desired, it is often given at a reduced dose and/or over a longer period of time. Based on published information in several clinical trials, this is an accepted practice at other institutions as well.[27,28,30,31]

Unlike propofol, benzodiazepines, or barbiturates, dexmedetomidine has little to no anticonvulsant effects.[33] The lack of anticonvulsant effects is important to remember when using dexmedetomidine

for patients experiencing alcohol withdrawal, as they may be at risk for developing seizures. At NCMC, a low-dose intermittent benzodiazepine is available as a scheduled and/or as needed rescue medication for patients experiencing alcohol withdrawal on dexmedetomidine who may be too sedated to trigger symptom treatment based on a traditional scoring system such as the CIWA-Ar. Furthermore, this practice allows for easier transition from a dexmedetomidine infusion back to a CIWA-Ar benzodiazepine treatment protocol.

In addition to being a retrospective review, other limitations exist in this study. Over the long period of data collection (2002-2009), there were possibilities for changes in the ICU standard of care that may account for variation in the primary endpoints. Use of the CIWA-Ar scoring system was not implemented until December 2007, which resulted in 13 patients not having CIWA-Ar scores at the time of ICU admission. Comorbidities were not controlled for and may have accounted for increased ICU length of stay and/or increased risk for intubation in patients experiencing alcohol withdrawal. Patients also received varying doses of intermittent analgesics, antipsychotics, and benzodiazepines that were not controlled for due to the nature of this retrospective study.

This study compared a dexmedetomidine infusion to a propofol infusion and/or a lorazepam infusion. Propofol and lorazepam were combined into one group, because the individual therapies or the combination of both was considered the standard of care for agitated, alcohol withdrawal patients admitted to the ICU at NCMC prior to 2008. Uniting patients who received propofol and/or lorazepam into one group may have affected statistical correlations; however, the goal of the study was to compare the current standard of care with the previous standard of care.

Furthermore, dexmedetomidine, propofol, and lorazepam dosing varied over the study period. Some patients received a bolus during initiation of dexmedetomidine therapy, whereas others did not. The decision to bolus with dexmedetomidine was based on the patients' level of agitation and hemodynamic stability. During the study period, dexmedetomidine, propofol, and lorazepam doses were most often titrated to a target Motor Activity Assessment Scale (MAAS) score of 2 to 3, but this may have been variable depending on the degree of sedation desired.

In summary, dexmedetomidine use was associated with a decrease in the incidence of endotracheal intubation when used to sedate patients experiencing alcohol withdrawal. Patients were able to be transferred to a lower level of care faster, as well as to be discharged from the hospital sooner, when compared to those patients treated with propofol and/or lorazepam continuous infusions. Dexmedetomidine is an attractive alternative to other sedative agents, such as propofol and benzodiazepine infusions, in the management of the symptoms associated with alcohol withdrawal syndrome. A larger, prospective randomized controlled study evaluating the usefulness of dexmedetomidine compared to other sedative agents for this indication is necessary to confirm the results of this study.

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