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ORIGINAL RESEARCH & CONTRIBUTIONS

Treatment of Alcohol Withdrawal Syndrome with and without Dexmedetomidine

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ABSTRACT

Context: Studies suggest that dexmedetomidine—an intravenous central-acting α_2-adrenergic agonist that effectively reduces anxiety among critically ill patients—is being used in patients with severe alcohol withdrawal. However, evidence supporting its use is limited, and it is not approved for this indication.

Objective: To assess the effect of dexmedetomidine on severe alcohol withdrawal symptoms and to compare its use with benzodiazepines alone.

Design: A retrospective, cohort study of 77 patients admitted to the adult medical intensive care unit with severe alcohol withdrawal between January 1, 2009, and October 31, 2013.

Main Outcome Measures: The difference in lorazepam equivalents and Clinical Institute Withdrawal Assessment for Alcohol scores in the 24 hours before and after initiation of dexmedetomidine therapy.

Results: The frequency of dexmedetomidine use increased dramatically between 2009 and 2013 (16.7% vs 82.4%; $p = 0.01$). Initiation of dexmedetomidine therapy was associated with significant improvements in Clinical Institute Withdrawal Assessment for Alcohol scores over corresponding 24-hour intervals (14.5 vs 8.5; $p < 0.01$). Benzodiazepine use also decreased, but the difference was not statistically significant at 24 hours ($p = 0.10$). Dexmedetomidine was well tolerated, requiring discontinuation of therapy in only 4 patients (10.5%). Dexmedetomidine use was also associated with significantly longer hospitalizations ($p < 0.01$).

Conclusion: Dexmedetomidine initiation was associated with a reduction in short-term alcohol withdrawal symptoms in patients in the intensive care unit, with only a few patients experiencing adverse events. However, its use was also associated with longer hospitalizations. Further research is necessary to evaluate whether dexmedetomidine is efficacious or cost-effective in severe alcohol withdrawal.

INTRODUCTION

Nearly 1 in 10 US adults meets the criteria for an alcohol use disorder, a condition that contributes to an estimated 79,000 deaths and $224 billion in societal costs each year.[1] Alcohol dependency also results in approximately 500,000 annual episodes of alcohol withdrawal that require pharmacologic treatment.[1] Alcohol withdrawal syndrome is characterized by adrenergic symptoms such as tremor, agitation, anxiety, and tachycardia. In severe cases, withdrawal can result in seizures, respiratory failure, and delirium tremens—a condition associated with inhospital mortality of 5%.[2]

Benzodiazepines are currently first-line therapy for treatment of alcohol withdrawal.[3] However, treatment with benzodiazepines may increase the risk of respiratory depression and sedation, especially in patients with liver dysfunction. There is also growing concern that benzodiazepines may worsen delirium and the mortality rate in hospitalized patients; therefore, recent guidelines recommend against using benzodiazepines as first-line sedatives in critical illness.[4-7] Prior studies suggest that dexmedetomidine—an intravenous central-acting α_2-adrenergic agonist that effectively reduces anxiety among critically ill patients—is being used in patients with severe alcohol withdrawal.[8-13] However, the evidence supporting its use is limited, and it has not received approval from the US Food and Drug Administration for this indication.[14]

We evaluated all episodes of severe alcohol withdrawal requiring admission to the intensive care unit (ICU) from January 1, 2009 to October 31, 2013, at Kaiser Permanente Santa Clara Medical Center in Santa Clara, CA. We also compared the baseline characteristics, hospital course, and outcomes of patients who received benzodiazepines alone versus those who also received dexmedetomidine.

Among patients with severe alcohol withdrawal, we evaluated whether dexmedetomidine initiation was associated with improved symptom control on the basis of Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar) scores[15] and decreased benzodiazepine use.

METHODS

The Kaiser Permanente institutional review board approved this retrospective study and waived the need for informed consent.

Subject Identification

We conducted a retrospective cohort study of patients with severe alcohol withdrawal who were admitted to the adult medical ICU at Kaiser Permanente

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Santa Clara Medical Center, a 327-bed community hospital with 30 ICU beds. We identified patients using International Classification of Disease, Ninth Revision diagnosis codes of 291.0, 291.3, and 291.81 for ICU admissions between January 1, 2009, and October 31, 2013. We excluded patients with a diagnosis of seizures unlikely to have resulted from alcohol withdrawal (Codes 780.31, 780.39, 345.0, 345.1, and 345.4-345.9). From this initial cohort, we excluded patients without alcohol withdrawal confirmed on manual chart review, those with brief ICU stays (< 20 minutes), those receiving dexmedetomidine therapy for diagnoses besides alcohol withdrawal, and those with incomplete documentation (Figure 1). Finally, we excluded patients with fewer than 5 CIWA score assessments documented in the medical record because these patients were believed to have less severe withdrawal symptoms. The CIWA score quantifies the severity of alcohol withdrawal on a scale of 0 through 67, with higher scores indicating more severe symptoms.[15] Our CIWA-Ar assessment is included in the Sidebar: Clinical Institute Withdrawal Alcohol Scale, Revised (CIWA-Ar) and Lorazepam Dosing Protocol Used at the Kaiser Permanente Santa Clara Medical Center, available online at www.thepermanentejournal.org/files/Spring2016/CIWA-Ar-Sidebar.pdf.

In our ICU setting, the Richmond Agitation Sedation Scale (RASS) is assessed in all patients at 4-hour intervals unless patients are receiving sedative medications, in which case RASS is assessed hourly. Thus, regarding intubated patients, if sedation was lightened to a RASS of 0 to -3, CIWA-Ar was assessed and lorazepam dosed accordingly. If the patient was sedated with RASS of -4, CIWA-Ar was not assessable, and thus lorazepam was dosed according to physician discretion. Patients' self-reported alcohol intake was estimated using nurses' and physicians' documentation in the medical record.

In our cohort, we grouped patients on the basis of whether they were treated with benzodiazepines alone or with benzodiazepines plus dexmedetomidine during their entire ICU stay. Dexmedetomidine therapy was not directed by a protocol.

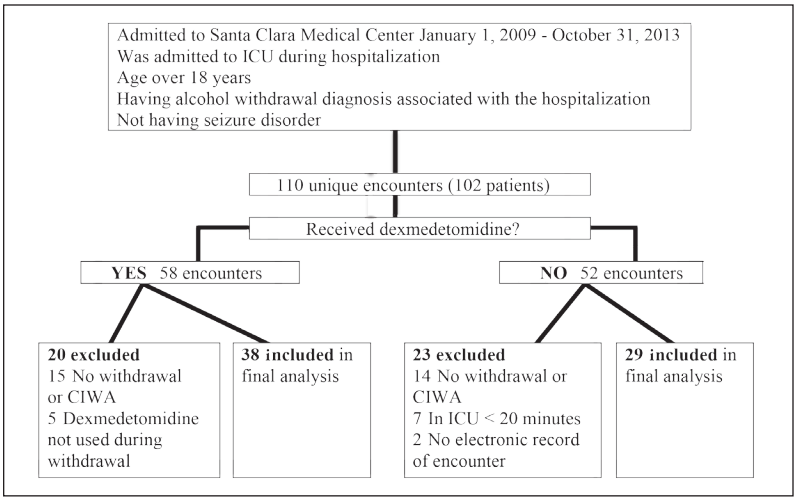

Figure 1. Flowchart of patients included in and excluded from study.

CIWA = Clinical Institute of Withdrawal Assessment; ICU = intensive care unit.

Patient Characteristics and Treatment

We recorded patients' baseline characteristics as well as their alcohol use and withdrawal history; we standardized self-reported alcohol intake on the basis of the National Institute of Alcohol Abuse and Alcoholism standard drink equivalent chart.[16] The ethanol level was first assessed at hospital admission. Delirium tremens information was obtained any time during the hospital course when the patient exhibited this sign. We evaluated patients' CIWA-Ar scores and quantified the timing and dosage of benzodiazepines and dexmedetomidine administered throughout the entire hospitalization. We standardized the doses of different benzodiazepines by converting all benzodiazepine doses into estimated lorazepam equivalents (Table 1).[17-18] At our center, a standardized CIWA-Ar protocol is used to administer symptom-based benzodiazepines with additional dosages of benzodiazepines administered on the basis of physician clinical judgment. For all patients in the ICU, dexmedetomidine is administered without a bolus and is titrated to a sedation target.

Analysis

Our primary outcome was the difference in lorazepam equivalents and CIWA-Ar scores in the 24 hours before and after the initiation of dexmedetomidine therapy. In secondary analysis, we compared the 30-day mortality and lengths of stay between patients receiving dexmedetomidine and benzodiazepines versus those receiving benzodiazepines alone. We reported variables as number (percentage) or median (interquartile range) and compared groups with the Wilcoxon signed rank test (paired) as well as the Wilcoxon rank sum test (unpaired). We considered a p value of < 0.05 to be statistically significant.

RESULTS

Baseline Patient Characteristics

We identified 38 patients treated with benzodiazepines and dexmedetomidine and 29 patients treated with

Table 1. Benzodiazepine equivalent conversions to lorazepam

Benzodiazepine	Dose equivalent, mg	Route of administration
Lorazepam	1.0	Oral, IV
Diazepam	5.0	Oral, IV
Chlordiazepoxide	12.5	Oral
Midazolam	2.0	IV
Clonazepam	2.0	Oral
Oxazepam	5.0	Oral

benzodiazepines alone who met entry criteria. Most characteristics between groups were not significantly different, with most patients in both groups having prior hospitalizations because of alcohol withdrawal (Table 2). However, patients treated with benzodiazepines alone were more likely to report multidrug abuse (34.5% vs 5.3%; p = 0.02) compared with patients treated with benzodiazepines and dexmedetomidine. The frequency of combined therapy for alcohol withdrawal increased dramatically over time from 16.7% (n = 1) in 2009 to 82.4% (n = 14) by 2013 (p = 0.01).

Cohort Comparison

Patients treated with combination therapy, compared with single-agent therapy, were more likely to have presented with severe alcohol withdrawal marked by delirium tremens (44.7% vs 20.7%; p = 0.02; Table 3). They were also more likely to have had a concomitant medical condition requiring critical care (23.7% vs 10.3%; p = 0.04). However, they were less frequently admitted directly to the ICU from the Emergency Department, as evidenced by a longer elapsed time between hospital and ICU admission (1.1 vs 0.3 days; p < 0.01). Most patients ultimately receiving dexmedetomidine did not receive it within the first 24 hours of hospitalization. In total, patients treated with combination therapy received significantly more benzodiazepines during their hospital course compared with those treated with single therapy (100.5 vs 37.0 lorazepam equivalent units; p < 0.01). Hospital and ICU length of stay (8.9 days vs 4.7 days; p < 0.01; and 2.9 days vs 1.4 days, p < 0.01, respectively) were also significantly higher in patients receiving combination therapy (p < 0.01 for both) compared with benzodiazepine alone, whereas mortality was not statistically different between groups (2.6% vs 6.9%; p = 0.56).

Effectiveness and Safety of Dexmedetomidine

The initiation of dexmedetomidine was associated with significant improvements in mean CIWA scores during corresponding 24-hour intervals (14.5 vs 8.5; p < 0.01; Figure 2, Table 3). Although overall benzodiazepine use also decreased, the difference was not statistically significant at 24 hours (p = 0.10; Figure 3). However, some patients experienced substantial reductions in benzodiazepine use after initiation of combination therapy; for example, 31.6% of patients experienced at least a 50% reduction in benzodiazepine use. Two patients had a reduction in lorazepam dose greater than 100 mg, whereas another patient required no additional

Table 2. Baseline patient characteristics[a]

Characteristic	Benzodiazepines alone (n = 29)	Benzodiazepines plus dexmedetomidine (n = 38)	p value
Median age, years (interquartile range)	51.0 (44-63)	54.5 (44.8-59.5)	0.89
Women	7.0 (24.1)	5.0 (13.2)	0.56
Previous hospitalizations for alcohol withdrawal	17.0 (58.6)	21.0 (55.3)	0.52
Multidrug abuse	10.0 (34.5)	2.0 (5.3)	0.02
Intubated	6.0 (20.7)	10.0 (26.3)	0.32
Self-reported alcohol intake			
Drinks per day (interquartile range)	11.0 (5.0-22.0)	12.0 (11.0-18.3)	0.32
Number of patients with data	29.0 (100)	35.0 (92.1)	
Year of hospitalization			
2009	5.0 (17.2)	1.0 (2.6)	0.01
2010	8.0 (27.6)	4.0 (10.5)	
2011	7.0 (24.1)	6.0 (15.8)	
2012	6.0 (20.7)	13.0 (34.2)	
2013 (until Oct 31)	3.0 (10.3)	14.0 (36.8)	

[a] Values are expressed as median number (percentage) unless otherwise indicated.

Table 3. Patient hospitalization characteristics: utilization and mortality

Characteristic	Benzodiazepines alone (n = 29)[a]	Benzodiazepines plus dexmedetomidine (n = 38)[a]	p value
Hospital admit time to ICU admit time, days	0.3 (0.2-0.6)	1.1 (0.4-1.7)	< 0.01
Direct admission to ICU from ED, no. (%)	21.0 (72.4)	20.0 (52.6)	0.88
Hospital length of stay, days	4.7 (3.5-8.9)	8.9 (6.1-12.0)	< 0.01
ICU length of stay, days	1.4 (0.6-2.3)	2.9 (1.8-5.4)	< 0.01
Delirium tremens,[b] no. (%)	6.0 (20.7)	17.0 (44.7)	0.02
Reason for ICU admission, no. (%)			
Alcohol withdrawal alone	16.0 (55.2)	25.0 (65.8)	0.04
Alcohol withdrawal plus medical condition	3.0 (10.3)	9.0 (23.7)	
Medical condition alone	10.0 (34.5)	4.0 (10.5)	
Ethanol level: not measured, no. (%)	11.0 (37.9)	15.0 (39.5)	0.43
Ethanol level[c]: measured, no. (%)			
> 0.3% (coma)	7.0 (24.1)	6.0 (15.8)	0.19
0.08%-0.3%	5.0 (17.2)	2.0 (5.3)	
0.01%-0.08% (legal limit)	1.0 (3.5)	3.0 (7.9)	
< 0.01% (unmeasurable)	5.0 (17.2)	12.0 (31.2)	
Lorazepam equivalents			
Throughout ICU stay,[d] mg	37.0 (16-85.5)	100.5 (48.8-193.1)	< 0.01
Patients with data, no. (%)	29.0 (100)	38.0 (100)	
30-day mortality, no. (%)	2.0 (6.9)	1.0 (2.6)	0.56
30-day mortality related to alcohol withdrawal, no. (%)	1.0 (3.4)	1.0 (2.6)	

[a] Values are expressed as median (interquartile range) unless otherwise indicated.
[b] Delirium tremens information was obtained any time during the hospital course when the patient exhibited this sign.
[c] Ethanol level was first assessed at hospital admission.
[d] Before, during, and after initiation of dexmedetomidine therapy.
ED = Emergency Department; ICU = intensive care unit.

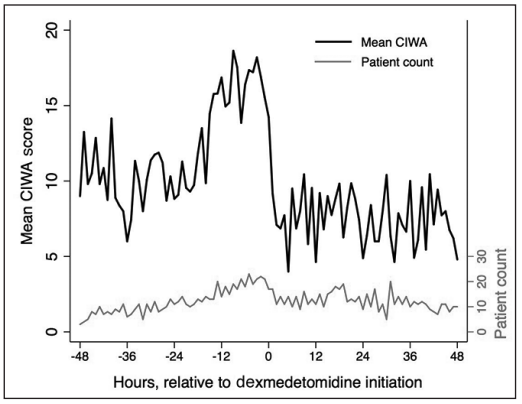

Figure 2. Mean scores of Clinical Institute of Withdrawal Assessment (CIWA) relative to hours before and after initiation of dexmedetomidine therapy (Time zero, x-axis).

The CIWA scores declined in the 24 hours after dexmedetomidine initiation compared with 24 hours before ($p < 0.01$). Gray line at bottom represents the number of patients who had scores corresponding to times during the hospital stay.

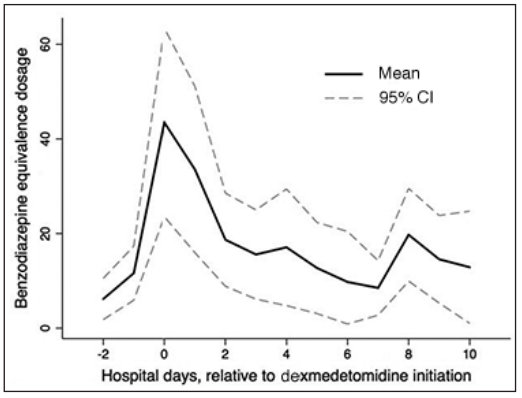

Figure 3. Mean benzodiazepine equivalents relative to initiation of dexmedetomidine therapy in days (Time zero, x-axis).

The difference in amount of benzodiazepines (in milligrams) used 24 hours before and 24 hours after the initiation of dexmedetomidine was not significant ($p = 0.10$).
CI = confidence interval.

lorazepam after initiation of dexmedetomidine therapy. Dexmedetomidine was well tolerated, with 4 (10.5%) of the patients requiring discontinuation of therapy because of hypotension or bradycardia.

DISCUSSION

In this study, we found that the initiation of dexmedetomidine was associated with a significant reduction in alcohol withdrawal symptoms. Dexmedetomidine use was also associated with minimal side effects, with only 10% of patients requiring discontinuation of therapy because of adverse events. Over time at our center, the concomitant use of dexmedetomidine and benzodiazepines increased dramatically, such that by 2012, more than two-thirds of ICU patients with alcohol withdrawal were treated with combination therapy. At the same time, we found that length of stay was significantly longer among patients treated with combination therapy compared with those treated with benzodiazepines alone. However, because of our retrospective study design, we could not determine whether this difference resulted from dexmedetomidine treatment itself or from residual confounding based on patient characteristics or the timing and initiation of therapy between groups.

The evidence supporting the use of dexmedetomidine in alcohol withdrawal is limited. To our knowledge, there is only 1 prospective study of dexmedetomidine use in alcohol withdrawal.[8] Mueller et al[8] randomly assigned 24 patients with CIWA scores of 15 or higher despite at least 16 mg of lorazepam over a 4-hour period to 1.2 μg/kg/h (high dose), 0.4 μg/kg/h (low dose), or placebo. The authors found that dexmedetomidine at either dose had a short-term benzodiazepine-sparing effect. However, this effect was no longer significant when evaluated over the total duration of hospitalization. Interestingly, dexmedetomidine administration also resulted in a slightly increased hospital length of stay, albeit not statistically significant. Furthermore, there were more cardiovascular side effects compared with benzodiazepine use alone. Smaller retrospective studies show similar findings to those of our study, suggesting that initiation of dexmedetomidine therapy was associated with reduced symptoms, benzodiazepine requirements, hypertension and tachycardia, and minimal side effects. Other reports also suggest that dexmedetomidine is effective in benzodiazepine-refractory alcohol withdrawal.[9-13]

Because of the adrenergic etiology of alcohol withdrawal syndrome, centrally acting α-agonists have the potential to help control symptoms.[19] The proposed mechanism of action is presynaptic α-agonistic activity, which prevents the further release of norepinephrine, thereby reducing anxiety, tachycardia, and tremor associated with alcohol withdrawal. The importance of dexmedetomidine use in comparison with standard-of-care benzodiazepine use is twofold. Because dexmedetomidine does not act on γ-aminobutyric acid receptors such as benzodiazepines, it does not suppress respiration; nor does it cause a decline in neurologic status, thus also reducing the risk of respiratory depression. The α-agonist activity of dexmedetomidine also makes it an appealing choice because it targets a separate pathway, which can increase the chance of treatment success.

Despite these potential benefits, dexmedetomidine also has limitations. Many patients experience cardiovascular side effects; for example, in large-scale studies of critically ill patients receiving

Table 4. Usage and effects of dexmedetomidine

Dexmedetomidine parameter	Number[a]
Total number of patients	38
CIWA score 24 hours *before* initiation (n = 36)	14.5 (9.3-17.3)[b]
CIWA score 24 hours *after* initiation (n = 37)	8.5 (5.5-11.2)[b]
Duration of dexmedetomidine, hours	37.4 (21.1-126.7)
Lorazepam equivalents	
Equivalents 24 hours before initiation	21.0 (5.0-56.9)[c]
Equivalents 24 hours after initiation	11.0 (3.3-33.3)[c]
Time to initiation, days	
From ICU admission	0.3 (0.1-1.1)
From hospital admission	1.7 (0.9-2.1)
From last drink (approximate)	2.5 (1.3-4)
Reason for discontinuation, no. (%)	
Improvement of withdrawal symptoms	20.0 (52.6)
Extubation	7.0 (18.4)
Hypotension/bradycardia	4.0 (10.5)
Death/transfer from hospital	4.0 (10.5)
Evaluation of mental status	3.0 (7.9)

[a] Values expressed as median (interquartile range) unless otherwise indicated.
[b] $p < 0.01$.
[c] $p < 0.10$.
CIWA = Clinical Institute Withdrawal Assessment; ICU = intensive care unit.

dexmedetomidine, approximately 25% experienced hypotension and 5% experienced bradycardia.[14] This may be a less important issue among patients with alcohol withdrawal who are hypertensive. Also, the relatively high cost of dexmedetomidine may limit its cost-effectiveness, especially because its impact on resource utilization (length of stay) and mortality were equivalent to, or worse than, benzodiazepine therapy alone. According to standardized pricing data, the average wholesale price of a 400 μg/100 mL vial of dexmedetomidine is $41.88 compared with $0.89 for a 2 mg/mL vial of lorazepam.[20] Thus, a daily infusion of 0.8 μg/kg/h for a 70-kg patient could purchase roughly 320 mg of lorazepam.

This study has several limitations. First, the study was performed at a single center and may reflect unique practice patterns and patient case mix, limiting generalizability. Second, although we included data from five years, we were able to capture only a modest population of patients with severe alcohol withdrawal, also limiting the power of our statistical analyses. Third, the study is vulnerable to confounding by indication because the initiation, titration, and discontinuation of dexmedetomidine and benzodiazepines were not controlled. For example, we noted several baseline differences between the cohorts, including differences in the severity of withdrawal symptoms and comorbid illness, the year in which they were treated, the disparity in the incidence of polysubstance abuse, and differences in the time of dexmedetomidine use. In addition, it is clear that the study captured patients during a period in which the use of dexmedetomidine was changing dramatically. Thus, in several patients treated with dexmedetomidine, alcohol withdrawal was not the primary diagnosis for ICU patients. Finally, we did not account for the use of other neurotropic agents, including antipsychotics, anticonvulsants, and pain medication, that can affect the progression of alcohol withdrawal and are increasingly used in ICU settings.

CONCLUSION

Dexmedetomidine initiation was associated with a reduction in short-term alcohol withdrawal symptoms in ICU patients, with only a fraction of patients experiencing adverse events. However, dexmedetomidine was associated with increases in both hospital and ICU length of stay. Given the increasing use of dexmedetomidine in patients with severe alcohol withdrawal, further research is necessary to determine whether its use is efficacious and cost-effective. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

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