Kalabalik and Sullivan. Int J Crit Care Emerg Med 2014, 1:1
ISSN: 2474-3674

International Journal of
Critical Care and Emergency Medicine

Review Article: Open Access

Use of Dexmedetomidine in the Management of Alcohol Withdrawal Syndrome in Critically Ill Patients

Julie Kalabalik* and Jesse B. Sullivan

Fairleigh Dickinson University School of Pharmacy, USA

***Corresponding author:** *Julie Kalabalik, Assistant Professor of Pharmacy Practice, Fairleigh Dickinson University School of Pharmacy, New Jersey, USA, Tel: 973-443-8428, Email: juliek@fdu.edu*

Abstract

Dexmedetomidine, an intravenous alpha$_2$-adrenergic agonist, is indicated for sedation of mechanically ventilated patients in the intensive care setting and sedation of non-intubated patients prior to or during surgical procedures. Dexmedetomidine targets presynaptic activation of the alpha$_2$-adrenergic receptor leading to inhibition of norepinephrine release and sympatholysis via activation of postsynaptic alpha$_2$-adrenergic receptors and may be useful in decreasing autonomic hyperactivity associated with alcohol withdrawal syndrome. With pharmacological characteristics including rapid onset, lack of respiratory depression, and short duration of action, dexmedetomidine has been used to manage alcohol withdrawal symptoms but data is limited. More recently, several studies have been published comparing dexmedetomidine to benzodiazepines or other sedatives in the management of alcohol withdrawal syndrome. In light of recent evidence, the purpose of this article is to provide the clinician with a review of the literature surrounding the safety and efficacy of dexmedetomidine in the management of alcohol withdrawal syndrome in critically ill patients.

Introduction

Alcohol consumption plays a role in the development of over 200 diseases and conditions in individuals worldwide, including liver cirrhosis, cancers, traumatic injury, and alcohol dependence [1]. In hospitalized patients with alcohol use disorders (AUD), up to 25% will develop acute alcohol withdrawal syndrome (AWS) [2]. In critically ill patients, presence of AWS is associated with increased duration of mechanical ventilation, prolonged intensive care unit (ICU) length of stay (LOS), more frequent infectious complications and higher mortality [3]. AWS is characterized by cessation of or reduction in heavy prolonged alcohol use plus 2 or more symptoms, causing clinically significant distress, or impairment of function. Symptoms include autonomic hyperactivity such as sweating or tachycardia, tremor, insomnia, nausea, vomiting, hallucinations, agitation, anxiety, or generalized tonic-clonic seizures [4]. Signs and symptoms of AWS may develop in as little as 6 hours after the initial decline from peak intoxication in alcohol dependent patients, peak at 48-72 hours, and improve after 4-5 days [4,5]. Left untreated, AWS may result in mortality in up to 15% of patients [2,6].

Alcohol exerts its depressant effects on the CNS via activation of the inhibitory γ-aminobutyric acid (GABA) pathways and inhibition of excitatory *N*-methyl-D-aspartate (NMDA) pathways. Prolonged repeat exposure to sufficient quantities of alcohol will result in down regulation of $GABA_A$ receptors and upregulation of NMDA receptors. Upon cessation of or reduction in alcohol intake, overstimulation of NMDA and under stimulation of $GABA_A$ results in an excitatory state producing AWS symptoms [7].

Clinical presentation of AWS can be divided into four stages. Stage one consists of autonomic hyperactivity within 6-8 hours of last alcohol intake [8]. About 25% of AWS patients will progress to stage two, identified by the presence of hyperactivity, insomnia, and/or visual hallucinations occurring 10-30 hours after last drink. Approximately 3-10% of AWS patients reach stage three, marked by neuronal excitation resulting in generalized tonic-clonic seizures [8,9]. The fourth stage of AWS is alcohol withdrawal delirium (AWD), commonly known as delirium tremens (DT), occurring in less than 5% of patients. Death typically results from hyperthermia, cardiac arrhythmias, complications of seizures, or underlying illness [10].

Recognition of AWS is vital as prompt treatment can prevent progression to severe complications [11]. The revised Clinical Institute Withdrawal Assessment for Alcohol score (CIWA-Ar) is a validated tool to assist in the early detection of AWS and may also be used to assess symptom severity and titrate pharmacologic therapy [12,13]. CIWA-Ar requires the participation of the subject for accurate results, making it inappropriate for patients unable to communicate, such as severely agitated or mechanically ventilated patients [14]. Other score systems such as the Sedation Agitation Score (SAS) or the Richmond Agitation Sedation Score (RASS) have been used in place of CIWA-Ar to titrate pharmacologic therapy in ICU patients [2,15,16].

Pharmacological management of AWS aims to correct the hyperactive excitatory state by replacing the inhibitory effect of alcohol with sedative agents. Benzodiazepines are considered drugs of choice, and work by modulating the binding of GABA to the $GABA_A$ receptor [17]. Benzodiazepines have been well studied in treating AWS and there is a lack of evidence to suggest other pharmacological agents are superior [18,19]. Guidelines for the management of AWD have been published over 10 years ago. Sedative-hypnotic agents are recommended as the drug of choice and the goal of pharmacotherapy is control of agitation [17]. Clinical practice guidelines for the management of pain, agitation, and delirium in critically ill patients recognize the importance of benzodiazepines in the management of

ClinMed International Library

Citation: Kalabalik J, Sullivan JB (2015) Use of Dexmedetomidine in the Management of Alcohol Withdrawal Syndrome in Critically Ill Patients. Int J Crit Care Emerg Med 1:002

Received: June 30, 2015: **Accepted:** July 27, 2015: **Published:** July 30, 2015

agitation in critically ill patients related to alcohol withdrawal and the lack of studies comparing the safety and efficacy of benzodiazepines versus dexmedetomidine in treating severe AWS [20].

Resistant AWS has been described as the need for >200mg of intravenous diazepam in the first 3-4 hours of therapy without achieving sedation goals [8]. Several adjunct therapies have been utilized in the treatment of AWS unresponsive to benzodiazepines alone. Phenobarbital is a sedative agent of the barbiturate class that works synergistically with benzodiazepines, activating $GABA_A$ via a different binding site as well as weakly inhibiting NMDA, but has a narrow therapeutic index and can cause significant respiratory depression [19]. Propofol an agent frequently used in ICU sedation activates $GABA_A$ and is a potent inhibitor of NMDA. A short half-life and predictable pharmacokinetic profile make it a promising agent for this purpose; however concerns exist regarding toxicities such as hypertriglyceridemia, and propofol infusion syndrome [14]. Neuroleptics such as haloperidol can be considered for resistant AWS; however, these agents should not be used alone as they are associated with increased mortality, longer duration of delirium, and increased complications [17]. β-blockers (e.g. propranolol) and α_2-agonists (e.g. clonidine) have been studied in combination with benzodiazepines, and may be useful for controlling symptoms of autonomic hyperactivity such as tachycardia and hypertension. These agents should not be used as monotherapy since they do not target the underlying cause of AWS and may mask symptoms resulting in under dosing of sedatives [14]. Dexmedetomidine, an intravenous $alpha_2$-adrenergic agonist, has been used to manage alcohol withdrawal symptoms. Recently, several studies have been published evaluating the efficacy of dexmedetomidine as adjunctive treatment in critically ill patients with AWS. The purpose of this article is to provide the clinician with a concise summary of current literature surrounding the use of dexmedetomidine in the management of alcohol withdrawal in critically ill patients.

Pharmacological Characteristics of Dexmedetomidine

Dexmedetomidine hydrochloride (Precedex®) is an $alpha_2$-adrenergic agonist approved by the Food and Drug Administration (FDA) in 1999 for sedation of mechanically ventilated patients during treatment in the intensive care unit. Dexmedetomidine is approved for continuous infusion not to exceed 24 hours according to manufacturer labeling. The drug is also approved for sedation in non-intubated patients for the initiation and maintenance of procedural sedation [21]. Dexmedetomidine possesses selective $alpha_2$-adrenergic agonist activity. Although dexmedetomidine is structurally and pharmacologically similar to clonidine, it is 8 times more selective for $alpha_2$-receptors [21,22]. The mechanism of action of dexmedetomidine involves presynaptic activation of the $alpha_2$-adrenergic receptor leading to inhibition of norepinephrine release and sympatholysis via activation of postsynaptic $alpha_2$-adrenergic receptors [22]. Dexmedetomidine produces analgesic, sedative, and anxiolytic effects [23]. It lacks activity on GABA or opioid receptors and is not associated with respiratory depression [24]. The terminal elimination half life is approximately 2 hours. The pharmacokinetics of dexmedetomidine are unaffected by renal impairment, and drug clearance is reduced in patients with hepatic impairment. Dose reduction is suggested for elderly patients and those with hepatic impairment. For sedation of an adult critically ill patient, dexmedetomidine is initially dosed at 1 mcg/kg over 10 minutes as a loading dose followed by a maintenance infusion of 0.2 – 0.7mcg/kg/hr. Most common adverse reactions include hypotension, dry mouth, and bradycardia. Transient hypertension has been observed with administration of the loading dose [21].

Literature Review of Dexmedetomidine for Alcohol Withdrawal

Several case reports have been published suggesting the role of dexmedetomidine for alcohol withdrawal as an adjunctive treatment which decreases autonomic hyperactivity, prevents intubation, and is benzodiazepine sparing [25-27]. In a case series involving 8 ICU patients with DT, all patients received dexmedetomidine bolus 1mcg/kg and continuous infusion 0.2 – 1mcg/kg/hr in addition to benzodiazepines and achieved adequate sedation and hemodynamic control without need for mechanical ventilation [28]. In a retrospective case series of 10 critically ill patients diagnosed with AWS, dexmedetomidine was administered with a mean infusion rate of 0.63mcg/kg/hr and mean infusion time of 92.7 hours. Three patients were managed with dexmedetomidine monotherapy and required intubation. A reduction in autonomic hyperactivity was reported, and no mortality, seizures, or aspiration pneumonia was reported [29]. In a retrospective chart review of 10 nonintubated ICU patients with severe alcohol withdrawal or AWD treated with dexmedetomidine, CIWA scores improved significantly (26 vs. 13; p=0.014) following dexmedetomidine initiation. Use of diazepam decreased significantly in the 24 hours post-dexmedetomidine initiation (13mg/hr vs. 3mg/hr; p=0.013). The average rate of dexmedetomidine infusion was 0.7mcg/kg/hr. Half of patients experienced hypotension, and no patients required intubation [30]. Prieto et al. conducted a retrospective chart review of 19 alcohol withdrawal ICU patients who failed benzodiazepine therapy alone or in combination with other sedatives and received dexmedetomidine. The median infusion rate was 0.34mcg/kg/hr and 6 patients received dexmedetomidine while intubated. Out of 19 patients, 13 (68%) were successfully treated with dexmedetomidine, resulting in extubation and/or control of alcohol withdrawal symptoms. Three patients (16%) did not experience resolution of agitation. Two patients (11%) developed hypotension requiring discontinuation of dexmedetomidine [31]. In a case series describing 5 ICU patients with alcohol withdrawal, dexmedetomidine was added as adjunctive treatment to benzodiazepines. Benzodiazepine usage initially increased after dexmedetomidine was initiated, but decreased by the second day of dexmedetomidine treatment in 4 out of 5 patients. A decrease in mean heart rate by 18% was observed after dexmedetomidine initiation, and no patients required intubation [32].

Rayner et al. conducted a retrospective analysis of 20 ICU patients with benzodiazepine-refractory alcohol withdrawal treated with dexmedetomidine. The decision to initiate dexmedetomidine was determined by the intensivist and no specific protocol for dexmedetomidine use for alcohol withdrawal existed. The investigators evaluated dosing of dexmedetomidine, benzodiazepines, haloperidol, alcohol withdrawal score, intubation, ICU LOS, systolic blood pressure, heart rate, number of hours spent with heart rate <60 or >100 beats per minute, and hours with systolic blood pressure < 90 or > 140 mmHg. Out of 17patients, a 61.5% decrease in benzodiazepine dose was noted in the 24 hours following dexmedetomidine initiation compared to the 24 hours prior to dexmedetomidine (20.3mg vs. 52.7mg; 95%CI, 16.7 – 48.1; p<0.001). A mean decrease of 1.9 points (21.1%) was observed within 24 hours following dexmedetomidine initiation in 11 patients for alcohol withdrawal severity scale (95% CI, 0.44 – 3.36; p<0.015).A significant decrease in heart rate was observed following dexmedetomidine initiation (before 102.8 vs. after 79.3 beats/min; 95% CI, 18.4 – 28.4; p<0.001). Time spent with heart rate > 100 beats/min also decreased (before 13.3 vs. after 2.3 hours (95% CI, 7.4 – 14.4; p<0.001). Average systolic blood pressure also decreased (before 140.2 vs. after 126.7mmHg; 95% CI, 5.32 – 21.68; p=0.002) and hours spent with systolic blood pressure > 140 mmHg decreased (before 11 vs. after 6.3 hours; 95% CI, 0.8 – 8.6; p=0.02). One patient out of 20 required intubation. Mean dexmedetomidine dose utilized was 0.53mcg/kg/hr and mean duration of dexmedetomidine therapy was 49.1 hours. The limitation of this study includes dexmedetomidine initiation at clinician discretion [33].

In a multicenter retrospective cohort study, Crispo et al. compared efficacy and safety outcomes in nonintubated patients with severe AWS who received either a benzodiazepine or dexmedetomidine continuous infusion in addition to standard medical therapy. Exclusion criteria included: intubation prior to study initiation or concurrently with study drug initiation, history of seizure disorder or previous alcohol withdrawal hospital admission within the last 30 days. Primary outcome was a composite end point of respiratory depression

requiring intubation or alcohol withdrawal seizures. Secondary outcomes were RASS score, duration of continuous infusion, benzodiazepine dose prior to and during study drug administration, hospital LOS, all-cause in-hospital mortality, and adverse events. Prior to study drug initiation, patients in the benzodiazepine group received significantly higher median total dose of benzodiazepines compared to the dexmedetomidine group (17mg vs. 8mg; p<0.01) and a greater percentage of patients in the benzodiazepine group received adjunctive olanzapine (54.5% vs. 10.7%; p<0.01). The median infusion rate of the benzodiazepine group in lorazepam equivalents was 2.1mg/hr with a mean duration of 55 hours; the median infusion rate for the dexmedetomidine group was 0.54mcg/kg/hr with a mean duration of 60.4 hours. The cumulative dose of lorazepam equivalents during study drug administration was significantly greater in the benzodiazepine group compared to the dexmedetomidine group (105mg vs. 3.5mg; p<0.01). No significant difference between groups was noted in terms of the composite efficacy end point, respiratory distress requiring intubation, or alcohol withdrawal seizures. No significant difference was seen in achieving a RASS score <+1 within 24 hours of study drug administration. A significantly greater number of patients in the dexmedetomidine group experienced bradycardia (13 vs. 5; p<0.01) and hypotension (12 vs. 4; p<0.01). No significant differences in hospital LOS or mortality were observed. Limitations of this study included lack of consistent CIWA-Ar documentation, use of RASS score as a surrogate for CIWA-Ar, and lack of a standardized protocol leading to practice variation [34].

In a single-center retrospective controlled cohort study, VanderWeide et al. evaluated the influence of dexmedetomidine on benzodiazepine requirements in ICU patients with AWS. Adult ICU patients with a CIWA-Ar score of >8 who received >8mg of lorazepam or benzodiazepine equivalent within a 6 hour window based on a symptom-driven alcohol withdrawal protocol were included in this study. Patients excluded were those with ICU admission ordexmedetomidine use for reasons other than AWS, ICU stay <24 hours, patients who expired within 72 hours of ICU admission, alcohol withdrawal patients with CIWA score <8 and/or who received <8mg of lorazepam in a 6 hour window. Primary outcome was difference in total 12-hour benzodiazepine requirement following dexmedetomidine initiation. Secondary outcomes included difference in 24-hour benzodiazepine requirement, ICU and hospital LOS, mechanical ventilation, CIWA-Ar scores, hemodynamic changes within 24 hours, and use of other adjunctive medications. Safety outcomes included incidence of bradycardia and hypotension. Twenty patients were in the dexmedetomidine group and 22 patients in the control group. The mean dose of dexmedetomidine was 0.46mcg/kg/hr and median duration of treatment was 30.8 hours. There was a significant difference in the mean 12-hour benzodiazepine requirement between the dexmedetomidine group and control group (-20mg vs. -8.3mg; p=0.0455). No difference was found between both groups in terms of mean 24 hour benzodiazepine requirement, ICU LOS, hospital LOS, mechanical ventilation requirement, or CIWA-Ar score change at 24 hours post study drug initiation. Dexmedetomidine patients experienced significantly greater change in heart rate and blood pressure within 24 hours following dexmedetomidine initiation. Limitations of this study include the creation of an inflection point, or time of drug initiation, for the control group, which is not validated [35].

Lizotte et al. compared dexmedetomidine to propofol in addition to an alcohol withdrawal order set and the impact on benzodiazepine and haloperidol requirements in a retrospective study. Adult patients with alcohol withdrawal receiving either dexmedetomidine or propofol and receiving the institution's alcohol withdrawal order set were included. Exclusion criteria included: scheduled antipsychotic or benzodiazepines from home, receiving dexmedetomidine and propofol concomitantly, alcohol withdrawal order set discontinued prior to sedative initiation, contraindication to benzodiazepines or antipsychotics, or receiving dexmedetomidine or propofol within 4 hours of being admitted to the hospital. The institution's alcohol withdrawal protocol based lorazepam dosing on Alcohol Withdrawal Assessment Scale (AWAS) score. Haloperidol was used as needed for severe agitation. The initiation of dexmedetomidine or propofol was based on clinician judgment. The primary outcome was benzodiazepine and haloperidol dosing before and after dexmedetomidine or propofol initiation. Secondary outcomes included AWAS score, ICU LOS, intubation, analgesic usage, RASS score, CAM-ICU score, and incidence of hypotension and bradycardia. Forty-one patients were included in the analysis. In the dexmedetomidine group, benzodiazepine use significantly decreased when comparing the 24 hours before and after drug initiation (before 20.9mg vs. after 4.4mg; $p \leq 0.0001$). Haloperidol use also decreased following dexmedetomidine initiation (before 8.5mg vs. after 0.7mg; p=0.043). Benzodiazepine and haloperidol use also significantly decreased following propofol initiation. No significant differences were observed between both groups in benzodiazepine use and haloperidol use. Mean AWAS and RASS scores decreased following dexmedetomidine initiation. Only 6 patients were assessed via CAM-ICU method and all 6 were positive for ICU delirium prior to sedation initiation. Only 1 patient had resolution of delirium following dexmedetomidine administration. No differences in analgesic use or ICU LOS were noted between both groups. When intubation was necessary, duration of intubation was shorter in the dexmedetomidine group compared to the propofol group (19.9 hours vs. 97.6 hours; p=0.002). Six patients in the dexmedetomidine group developed bradycardia and hypotension. Two propofol patients developed hypotension and no patients developed bradycardia. Limitations in this study include use of AWAS score and lack of review of average dose for all patients [36].

Frazee et al. evaluated 33 critically ill adult patients with AWS treated with dexmedetomidine in a retrospective case series. Adult patients included in the analysis were admitted to the ICU with a diagnosis of AWS, received at least 1 dose of a benzodiazepine prior to or on ICU admission, had at least 1 CIWA-Ar score within 24 hours of ICU admission, and were initiated on dexmedetomidine. Exclusion criteria included: those whose primary diagnosis was not alcohol withdrawal, concurrent traumatic brain injury or intracranial hemorrhage, ICU admission <24 hours, clonidine administration in the 12 hours before or during dexmedetomidine infusion, or admission from a correctional facility. Utilization and dose of benzodiazepines and dexmedetomidine were dependent on provider preference. The primary end point was the difference in total benzodiazepine requirement in the 12 hours before and after dexmedetomidine initiation. Changes in hemodynamics and incidence of hypotension, hypertension, and bradycardia were documented. Secondary end points included need for mechanical ventilation, ICU LOS, new-onset seizure or pneumonia, and total benzodiazepine requirements. During the study period, patients received a median of 110mg of lorazepam equivalents and had a baseline median CIWA-Ar score of 15. Within 12 hours after initiating dexmedetomidine, benzodiazepine requirements decreased significantly with a median reduction of 20mg (p<0.001). A significant decrease in mean arterial pressure (108 mmHg vs. 94 mmHg; p=0.03) and heart rate (116 beats/min vs. 99 beats/min; p<0.001) was observed as well. While receiving dexmedetomidine, 4 patients (12%) experienced hypotension and6 patients (18%) experienced hypertension. Twenty-six patients (78%) received a maximum dexmedetomidine infusion rate 0.7mcg/kg/hr or less. Eleven (33%) patients required mechanical ventilation, of which 4 patients were initiated on dexmedetomidine prior to intubation and 7 patients were initiated after intubation. Median hospital LOS was 7 days and ICU LOS was 3.1 days. Six patients (18%) developed pneumonia and 3 (9%) developed seizure. The limitations of this study include the lack of definition for severe refractory AWS, the inability to use alcohol withdrawal scoring systems in mechanically ventilated patients representing 33% of patients in this study, and the lack of standardization in dexmedetomidine utilization and dosing [37].

In a retrospective cohort study of 1760 adult ICU patients with AWS over a 5 year study period, investigators evaluated the incidence of hypotension and bradycardia amongst patients who received

dexmedetomidine as adjunctive therapy compared to those who received usual care. ICU LOS, whether patients were discharged home, and in-hospital mortality were also evaluated. No difference in rate of hypotension or bradycardia, in-hospital mortality, or percentage of patients discharged home was noted between groups. Patients who received dexmedetomidine had a significantly longer ICU LOS compared to patients who received usual care (8.3 days vs. 2.3 days; p<0.01) [38]. In March of 2015, Ludtke et al. published findings of a retrospective chart review of ICU patients experiencing alcohol withdrawal who received continuous infusion of dexmedetomidine, propofol, and/or lorazepam. Primary outcomes included ICU and hospital LOS and incidence and duration of mechanical ventilation. Fifteen patients received dexmedetomidine and 17 received propofol and/or lorazepam. Significantly less patients in the dexmedetomidine group required intubation and mechanical ventilation (13.3% vs. 58.8%; p=0.006). Both hospital LOS (135.8 hrs vs. 241.1 hrs; p=0.008) and ICU LOS (53 hrs vs. 114.9 hrs; p=0.016) were significantly less in the dexmedetomidine group. Limitations included lack of CIWA-Ar scores for 13 patients in the study, and lack of control for comorbidities or concomitant medications [39].

Tolonen et al. conducted a prospective observational study of 18 patients with AWD treated with dexmedetomidine in addition to benzodiazepines. Primary outcome was resolution of delirium according to CAM-ICU and RASS. The maximum dose of dexmedetomidine administered was 1.5mcg/kg/hr. The mean duration of dexmedetomidine treatment was 23.9 hours. The mean time to symptom resolution was 3.8 days. No patients in this study required intubation and no adverse effects of dexmedetomidine treatment were noted [40].

Mueller et al. conducted a single center, prospective, randomized, double blind, placebo-controlled trial evaluating the efficacy of dexmedetomidine as adjunctive treatment in addition to a standardized, symptom-triggered AWS protocol. The primary efficacy outcome was change in total lorazepam requirement within the first 24 hours after study drug initiation compared to the 24 hours prior to study drug initiation and cumulative lorazepam dose in the first 7 hospital days. The secondary efficacy outcomes included total and daily lorazepam dose following study drug initiation, occurrence of mild, moderate, or severe AWS, occurrence of agitation, and endotracheal intubation or seizure occurrence after study drug initiation. Primary safety outcomes included bradycardia, hypotension, and need for study drug rate adjustment due to hypotension or bradycardia. Twenty-four adult patients with severe AWS were included in this study. Severe AWS was defined as a CIWA score ≥ 15 despite 16mg or more of lorazepam over a period of 4 hours. Patients were admitted to the medical ICU and received standard treatment with a symptom-triggered AWS protocol. Patients with CIWA scores ≥ 15 were administered 2 – 4mg of IV lorazepam every 30 minutes. If the patient received ≥ 8mg of lorazepam within an hour, continuous infusion and adjunctive medications were ordered. Patients were randomized to receive high dose dexmedetomidine (1.2mcg/kg/hr), low dose dexmedetomidine (0.4mcg/kg/hr), or placebo in addition to the AWS protocol. The study drug was continued until the patient was no longer in withdrawal or up to 5 days. If a patient experienced hypotension or bradycardia, the study drug was temporarily discontinued or the infusion rate was adjusted. If the drug was discontinued due to hypotension or bradycardia, the infusion was restarted at half the original rate once the patient was stable. Comparing patients who received dexmedetomidine to placebo, no significant difference was noted in median lorazepam requirements 24 hours following study drug initiation. The dexmedetomidine group had a significant difference in 24-hour pre-post lorazepam requirement compared to placebo (-56.4mg vs. -8mg; p=0.037). The post-hoc analysis showed significant difference in 12-hour pre-post lorazepam requirement in the dexmedetomidine group compared to placebo (-36.5mg vs. -17.5mg; p=0.027). Lorazepam requirements within the first 7 days of hospitalization were similar in both dexmedetomidine and placebo groups. No significant differences were noted between high and low dose dexmedetomidine groups. No significant differences were observed between dexmedetomidine and placebo groups regarding proportion of patients with severe or moderate CIWA scores or ICU and hospital length of stay. Out of 24 patients, 11 were already intubated at study initiation. Four patients in the dexmedetomidine group experienced bradycardia versus no patients in the placebo group. Three patients in the dexmedetomidine group experienced hypotension versus no patients in the placebo group [41].

A prospective, randomized, double-blind, placebo-controlled, parallel-group study evaluating dexmedetomidine compared to placebo with rescue lorazepam in critically ill adults with severe AWS and AWD is currently recruiting participants. Inclusion criteria for this study are adult patients with severe AWS or AWD as per DSM-IV definition that require admission to the ICU for medical management. The primary outcome measure of this study is ICU LOS and secondary outcome measures include number of delirium-free and ventilator-free days within the first 28 days of hospitalization, hospital LOS, neurocognitive and quality of life scores at hospital discharge, cost, and adverse events. The estimated study completion date is September 2017 [42].

The addition of dexmedetomidine to standard care has been shown to decrease benzodiazepine requirement in critically ill patients with AWS. A significant decrease in lorazepam equivalents within the first 24 hours following dexmedetomidine initiation has been demonstrated without compromising symptom control in a small randomized controlled trial. Reductions in blood pressure and heart rate have been observed following dexmedetomidine initiation demonstrating the beneficial effect of the drug on autonomic hyperactivity symptoms associated with AWS. Although dexmedetomidine should not replace cornerstone benzodiazepine therapy for AWS, it represents a beneficial adjunctive drug with several advantages for patients demonstrating autonomic hyperactivity associated with severe alcohol withdrawal or in cases of inadequate response to benzodiazepine therapy. The impact of dexmedetomidine on hospital and ICU LOS, need for mechanical ventilation and delirium needs to be further elucidated through future research.

Conclusion

In comparison to other pharmacological agents used in the management of alcohol withdrawal, dexmedetomidine quickly decreases autonomic hyperactivity while avoiding respiratory depression. Although dexmedetomidine is not indicated for the treatment of alcohol withdrawal, literature to date shows that dexmedetomidine is a promising adjunct agent for the management of alcohol withdrawal symptoms, which has the potential to be benzodiazepine sparing. Further research is needed to fully elucidate the role of dexmedetomidine and its impact on clinical outcomes including need for mechanical ventilation, LOS, and mortality.

References

1. World Health Organization (2014) Global status report on alcohol and health - 2014 edn. Geneva, Switzerland: WHO Press.
2. Duby JJ, Berry AJ, Ghayyem P, Wilson MD, Cocanour CS (2014) Alcohol withdrawal syndrome in critically ill patients: protocolized versus nonprotocolized management. J Trauma Acute Care Surg 77: 938-943.
3. Spies CD, Dubisz N, Neumann T, Blum S, Müller C, et al. (1996) Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. Crit Care Med 24: 414-422.
4. Arlington VA (2013) Diagnostic and Statistical Manual of Mental Disorders. (5th edn). American Psychiatric Association.
5. Trevisan LA, Boutros N, Petrakis IL, Krystal JH (1998) Complications of alcohol withdrawal: pathophysiological insights. Alcohol Health Res World 22: 61-66.
6. Ungur LA, Neuner B, John S, Wernecke K, Spies C (2013) Prevention and therapy of alcohol withdrawal on intensive care units: systematic review of controlled trials. Alcohol Clin Exp Res 37: 675-686.
7. Carlson RW, Kumar NN, Wong-Mckinstry E, Ayyagari S, Puri N, et al. (2012) Alcohol withdrawal syndrome. Crit Care Clin 28: 549-585.
8. Perry EC (2014) Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs 28: 401-410.

9. Al-Sanouri I, Dikin M, Soubani AO (2005) Critical care aspects of alcohol abuse. South Med J 98: 372-381.

10. Schuckit MA (2014) Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med 371: 2109-2113.

11. Awissi DK, Lebrun G, Coursin DB, Riker RR, Skrobik Y (2013) Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary. Intensive Care Med 39: 16-30.

12. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989) Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 84: 1353-1357.

13. Kosten TR, O'Connor PG (2003) Management of drug and alcohol withdrawal. N Engl J Med 348: 1786-1795.

14. Sarff M, Gold JA (2010) Alcohol withdrawal syndromes in the intensive care unit. Crit Care Med 38: S494-501.

15. Gold JA, Rimal B, Nolan A, Nelson LS (2007) A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med 35: 724-730.

16. Weinberg JA, Magnotti LJ, Fischer PE, Edwards NM, Schroeppel T, et al. (2008) Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. J Trauma 64: 99-104.

17. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, et al. (2004) Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 164: 1405-1412.

18. Holbrook AM, Crowther R, Lotter A, Cheng C, King D (1999) Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ 160: 649-655.

19. Cooper E, Vernon J (2013) The effectiveness of pharmacological approaches in the treatment of alcohol withdrawal syndrome (AWS): a literature review. J Psychiatr Ment Health Nurs 20: 601-612.

20. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, et al. (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41: 263-306.

21. (2014) Precedex® [Lake Forest], IL: HospiraInc.

22. Gertler R, Brown HC, Mitchell DH, Silvius EN (2001) Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 14: 13-21.

23. Muzyk AJ, Fowler JA, Norwood DK, Chilipko A (2011) Role of Î±2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother 45: 649-657.

24. Hoy SM, Keating GM (2011) Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs 71: 1481-1501.

25. Darrouj J, Puri N, Prince E, Lomonaco A, Spevetz A, et al. (2008) Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. Ann Pharmacother 42: 1703-1705.

26. Rovasalo A, Tohmo H, Aantaa R, Kettunen E, Palojoki R (2006) Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. Gen Hosp Psychiatry 28: 362-363.

27. Maccioli GA (2003) Dexmedetomidine to facilitate drug withdrawal. Anesthesiology 98: 575-577.

28. Lebron Cooper, Daniel Castillo, Ricardo Martinez-Ruiz, Richard Silverman, Karen Hitchen (2005) Adjuvant use of dexmedetomidine may reduce the incidence of endotracheal intubation caused by benzodiazepines in the treatment of delirium tremens (abstract). Anesthesiology 103: A317.

29. DeMuro JP, Botros DG, Wirkowski E, Hanna AF (2012) Use of dexmedetomidine for the treatment of alcohol withdrawal syndrome in critically ill patients: a retrospective case series. J Anesth 26: 601-605.

30. Dailey RW, Leatherman JW, Sprenkle MD (2011) Dexmedetomidine in the management of alcohol withdrawal and alcohol withdrawal delirium. Am J Respir Crit Care Med 183: A3164.

31. Prieto MN, Barr J, Tanaka T, Davies F, Geller E (2007) Dexmedetomidine: a novel approach to the management of alcohol withdrawal in the ICU (abstract). Anesthesiology 107: 1313.

32. Muzyk AJ, Revollo JY, Rivelli SK (2012) The use of dexmedetomidine in alcohol withdrawal. J Neuropsychiatry Clin Neurosci 24: 45-46.

33. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF; Study Institution (2012) Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Ann Intensive Care 2: 12.

34. Crispo A, Daley MJ, Pepin JL, Harford PH, Brown CV (2014) Comparison of clinical outcomes in nonintubated patients with severe alcohol withdrawal syndrome treated with continuous infusion sedatives: dexmedetomidine versus benzodiazepines. Pharmacother 34: 910-917.

35. VanderWeide LA, Foster CJ, MacLaren R, Kiser TH, Fish DN, et al. (2014) Evaluation of Early Dexmedetomidine Addition to the Standard of Care for Severe Alcohol Withdrawal in the ICU: A Retrospective Controlled Cohort Study. J Intensive Care Med .

36. Lizotte RJ, Kappes JA, Bartel BJ, Hayes KM, Lesselyoung VL (2014) Evaluating the effects of dexmedetomidine compared to propofol as adjunctive therapy in patients with alcohol withdrawal. Clin Pharmacol 6: 171-177.

37. Frazee EN, Personett HA, Leung JG, Nelson S, Dierkhising RA, et al. (2014) Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients. J Crit Care 29: 298-302.

38. Brendan J. Clark, Marc Moss, Katie H. Overdier, Angela Keniston, Ellen L. Burnham, et al. (2012) Dexmedetomidine as an adjunctive therapy for critically ill patients with severe alcohol withdrawal syndrome (abstract). Am J Respir Crit Care Med 185: A3186.

39. Ludtke KA, Stanley KS, Yount NL, Gerkin RD (2015) Retrospective review of critically ill patients experiencing alcohol withdrawal: dexmedetomidine versus propofol and/or lorazepam continuous infusions. Hosp Pharm 50: 208-213.

40. Tolonen J, Rossinen J, Alho H, Harjola VP (2013) Dexmedetomidine in addition to benzodiazepine-based sedation in patients with alcohol withdrawal delirium. Eur J Emerg Med 20: 425-427.

41. Mueller SW, Preslaski CR, Kiser TH, Fish DN, Lavelle JC, et al. (2014) A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med 42: 1131-1139.

42. U.S. National Institutes of Health (2015) Dexmedetomidine (Precedex®) for severe alcohol withdrawal syndrome (AWS) and alcohol withdrawal delirium (AWD).