Original Article

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The Addition of Dexmedetomidine as an Adjunctive Therapy to Benzodiazepine Use in Alcohol Withdrawal Syndrome

A Literature Review

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Abstract

Alcohol withdrawal syndrome (AWS) is commonly encountered in the intensive care unit population. Currently, the mainstay treatment for AWS is the use of benzodiazepines. However, some patients are refractory to benzodiazepine treatment due to heavy alcohol abuse. In addition, escalating doses of benzodiazepines can lead to respiratory depression, requiring intubation and mechanical ventilation. Intubation and mechanical ventilation increase both intensive care unit and hospital length of stay. The addition of pharmacological agents to reduce the amount of benzodiazepine use in AWS has recently been studied. Most recently, the addition of dexmedetomidine, a selective α_2 adrenoceptor agonist, has been explored. Dexmedetomidine provides sedation without depressing the respiratory system, making it an ideal pharmacological agent to use. The addition of dexmedetomidine in adjunct to benzodiazepine use has been proven to reduce the amount of benzodiazepine administered, decrease the number of patients requiring intubation and mechanical ventilation, and decrease length of intensive care unit stay and overall length of hospital stay. However, the use of dexmedetomidine has also produced harmful side effects such as hypotension and bradycardia. The use of dexmedetomidine in conjunction with benzodiazepines in the setting of AWS is promising; however, more research needs to be conducted in regard to the safety and efficacy of its use.

Keywords: alcohol withdrawal syndrome, benzodiazepines, dexmedetomidine

INTRODUCTION

Alcohol is the most frequently abused drug within the United States. According to the National Institute on Alcohol Abuse and Alcoholism (2016), in 2014, 16.3 million adults aged 18 years and older were classified as having an alcohol use disorder. Nearly 88,000 people die each year from alcohol misuse, and in 2010, alcohol misuse costs the United States $249 billion (National Institute on Alcohol Abuse and Alcoholism, 2016). Approximately 40% of all hospitalized patients have a history of alcohol abuse, and an estimated 18% will experience alcohol withdrawal syndrome (AWS) during their hospital stay (Crispo, Daley, Pepin, Harford, & Brown, 2014). In addition, alcohol use disorders are associated with 9%–33% of intensive care admissions (Frazee et al., 2014). AWS begins as early as 8 hours after the last alcoholic beverage was consumed and typically peaks at 72 hours (Crispo et al., 2014). The early symptoms of AWS include agitation, anxiety, insomnia, tremors, nausea, abdominal pain, tachycardia, and hypertension. Of the patients who experience AWS, 5%–20% will progress to severe symptoms such as confusion, hallucinations, seizures, and delirium tremens and require an intensive care unit (ICU) stay (Crispo et al., 2014). Patients admitted to the ICU with AWS have an increased hospital and ICU length of stay, a longer duration of mechanical ventilation, higher costs, and increased mortality compared with those admitted without an alcohol-related disorder (Dixit et al., 2016). Currently, the gold standard for treating AWS is with benzodiazepines; however, they may cause oversedation leading to mechanical ventilation, which increases length of ICU and hospital stay. The purpose of this literature review was to explore whether the addition of dexmedetomidine therapy reduces the amount of benzodiazepine use, patients requiring mechanical ventilation, and length of ICU and hospital stay.

BACKGROUND

Ethanol's primary action on the central nervous system is mediated by the disruption of two neurotransmitter pathways: the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and the excitatory neurotransmitter glutamate, which binds to the N-methyl-D-aspartate (NMDA) receptor (Dixit et al., 2016). Alcohol mimics GABA's effects in the brain, which inhibits

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postsynaptic NMDA receptor activity. Exposure to alcohol leads to an increased activity of GABA at the GABA receptors. Concurrently, alcohol inhibits the excitatory action of glutamate at the NMDA receptor, which leads to sedative and central nervous system depression (Dixit et al., 2016). Chronic alcohol abuse leads to insensitivity to GABA. Therefore, more inhibitors are required to maintain inhibitory tone. In contrast, because alcohol inhibits the excitatory action of glutamate, adaption occurs by increasing the number of glutamate receptors (Hoffman & Weinhouse, 2016). Abrupt discontinuation of alcohol causes neuronal hyperactivity from overactivation of the NMDA pathway (Hoffman & Weinhouse, 2016). Overactivation of this pathway leads to the symptoms of AWS such as tremors, anxiety, tachycardia, and hypertension.

Traditionally, benzodiazepines have been the mainstay treatment for AWS. Benzodiazepines are GABA receptor agonists and therefore replace the neurodepressant activity of alcohol the brain is used to (Crispo et al., 2014). Benzodiazepines have been proven to reduce the recurrent rate of seizures by 21% in comparison with a placebo and decrease the risk of mortality when compared with neuroleptic agents (Crispo et al., 2014). Benzodiazepines are administered either on a scheduled around-the-clock base or based on the patient's symptoms. However, patients with considerable alcohol tolerance can show cross-tolerance to benzodiazepines leading to high-dose administration. High doses of benzodiazepines can lead to oversedation, respiratory distress requiring mechanical ventilation, an increased aspiration risk, an increased length of hospital stay, and an increased cost of hospitalization (Bielka, Kuchyn, & Glumcher, 2015). The addition of an adjunctive therapy to help decrease the amount of benzodiazepine administered could reduce the rate of oversedation, mechanical ventilation, length of hospital stay, and hospital cost. Several studies have been performed on the addition of dexmedetomidine as an adjunctive therapy to benzodiazepines in the management of AWS.

Dexmedetomidine is a highly selective α_2 adrenoceptor agonist that reduces noradrenaline release and produces sedation and anxiolysis (Muzyk, Kerns, Brudney, & Gagliardi, 2013). Unlike benzodiazepines, dexmedetomidine has no activity at the GABA or opioid receptors. Therefore, it provides sedation without respiratory compromise (Muzyk et al., 2013). Although dexmedetomidine does not directly treat underlying mechanisms of AWS, it does help control the sympathetic symptoms such as tremor, hypertension, and tachycardia. The addition of dexmedetomidine therapy in treating AWS could decrease the amount of benzodiazepines needed to control AWS symptoms, which would ultimately lead to decrease in oversedation, mechanical ventilation, and length of hospital stay.

METHODS

Currently, the use of benzodiazepines is the standard treatment for AWS. However, some patients require escalating doses of benzodiazepines, which can lead to intubation, mechanical ventilation, and an increased length of hospital stay. The addition of dexmedetomidine therapy may help decrease the amount of benzodiazepines needed to treat AWS. A literature search was conducted to review the current literature on the effects of the addition of dexmedetomidine therapy to benzodiazepine therapy in patients with AWS. The electronic databases searched included PubMed, UpToDate, and CINAHL. The key search terms included were "alcohol withdrawal syndrome," "dexmedetomidine and alcohol withdrawal," "alcohol withdrawal syndrome," and "intensive care unit," "management of alcohol withdrawal syndrome," "benzodiazepines and alcohol withdrawal syndrome," and "dexmedetomidine therapy." Next, the data were evaluated for inclusion. Inclusion criteria included published between January 2011 and October 2016, written in the English language, use of human subjects, applicable to the critical care setting, and relevant to the research focus. Studies were excluded if they were performed in an outpatient setting, were not performed in a critical care setting, or used animal subjects. Seven studies met the inclusion criteria. A summary of the included studies can be found in Table 1. Finally, the data were extracted from the primary sources and analyzed.

RESULTS

This literature review consisted of five retrospective studies and two randomized controlled studies. The targeted outcomes evaluated were a decrease in the total amount of "as needed" benzodiazepines doses, a decrease in the rate of respiratory distress and intubation, and a decrease in the length of ICU and hospital stay with the addition of a continuous infusion of dexmedetomidine. In addition, the safety of dexmedetomidine was evaluated because it can cause bradycardia and hypotension.

Crispo et al. (2014) performed a retrospective, multicenter cohort study that evaluated the clinical outcomes in 61 nonintubated patients being treated for severe AWS, requiring a continuous infusion of either dexmedetomidine or a benzodiazepine (lorazepam or midazolam), in addition to the standard medical therapy for AWS. The study evaluated the number of "as needed" doses of benzodiazepine required to treat AWS, in addition to the current infusions. In addition, the study evaluated the occurrence of respiratory distress requiring intubation and the length of ICU and hospital stay. Crispo et al. found that the benzodiazepine group required a median additional 105-mg "as needed" benzodiazepine doses versus the dexmedetomidine group, which needed an additional 3.5-mg "as needed" doses. In addition, it was hypothesized that the addition of dexmedetomidine therapy would reduce the number of incidences of respiratory distress requiring intubation. Although the occurrence of respiratory distress requiring intubation was lower in the dexmedetomidine group (BZD = 9.1% vs. DEX = 7.1%), it was not statistically significant ($p > .99$; Crispo et al., 2014). It was also determined that dexmedetomidine did not have an effect on the length of hospital stay (BZD = 9.7 days vs. DEX = 10.2 days; Crispo et al., 2014). During the study, the dexmedetomidine group experienced some adverse side effects, such as hypotension and bradycardia. Thirteen of the 28 experienced bradycardia, and 12 developed hypotension (Crispo et al., 2014).

TABLE 1	Summary of Studies That Compared the Addition of Dexmedetomidine With Standard Benzodiazepine Therapy in the Treatment of AWS
Study	Beg, M., Fisher, S., Siu, D., Rajan, S., Troxell, L., & Liu, V. (2016). Treatment of alcohol withdrawal syndrome with and without dexmedetomidine. *The Permanente Journal, 20*(2), 49–53. doi:10.7812/TPP/15-113
Purpose	To assess the effects of dexmedetomidine on severe alcohol withdrawal symptoms and compare its use with benzodiazepines alone.
Sample	Patients included in the study were those admitted to the adult medical ICU at Kaiser Permanente Santa Clara Medical Center with diagnosis codes of 291.0, 291.3, and 291.81 from January 1, 2009, to October 31, 2013. Patients were excluded if they had a diagnosis of seizures unlikely from alcohol withdrawal, if alcohol withdrawal syndrome was not accurately documented, if their ICU stay was brief (<20 minutes), if they were receiving dexmedetomidine therapy for reasons other than alcohol withdrawal, or if they have a documented Clinical Institute Withdrawal Assessment for Alcohol (CIWAA) score assessment of less than 5.
Measures	A retrospective cohort study was conducted. The patients' baseline characteristics as well as their alcohol use and withdrawal history were recorded. The self-reported alcohol intake was standardized on the basis of the National Institute of Alcohol Abuse and Alcoholism's standard drink equivalent. The ethanol level was first assessed at hospital admission. Delirium tremens information was obtained anytime during the hospital course when the patient exhibited this sign. The patients' CIWAA scores were evaluated and quantified the timing and dosage of benzodiazepines and dexmedetomidine administered throughout the entire hospitalization. The doses of different benzodiazepines were standardized by converting all benzodiazepine doses into estimated lorazepam equivalents. The primary outcome was the difference in lorazepam equivalents and CIWAA scores in the 24 hours before and after the initiation of dexmedetomidine therapy. In the secondary analysis, 30-day mortality and lengths of stay between patients receiving dexmedetomidine and benzodiazepines versus those receiving benzodiazepines alone were compared.
Findings	• The initiation of dexmedetomidine was associated with significant improvements in mean CIWAA scores during the corresponding 24-hour intervals.
	• Although overall benzodiazepine use also decreased, the difference was not statistically significant at 24 hours.
	• Some patients experienced substantial reductions in benzodiazepine use after the initiation of combination therapy.
	• Use of dexmedetomidine was associated with an increased length of hospital stay.
Study	Bielka, K., Kuchyn, I., & Glumcher, F. (2015). Addition of dexmedetomidine to benzodiazepines for patients with alcohol withdrawal syndrome in the intensive care unit: A randomized controlled study. *Annals of Intensive Care,5*(33), 36–42. doi:10.1186/s13613-015-0075-7
Purpose	To evaluate whether the addition of dexmedetomidine to benzodiazepine therapy is effective and safe for patients with alcohol withdrawal syndrome in the intensive care unit.
Sample	72 patients were included in this study. The study was conducted in the adult mixed ICU at the private hospital Boris in Kiev, Ukraine. Patients were included in the study if they were between the ages of 18 and 75 years and were going through alcohol withdrawal syndrome per the *Diagnostic and Statistical Manual of Mental Disorders*. Patients were excluded if they had a history of abuse of other psychoactive substances or of withdrawal states, general anesthesia within the previous 24 hours, other use of sedatives within the past 24 hours, severe neurological disorder, pregnancy or lactation, severe comorbidities (severe heart failure, myocardial infarction, liver failure, and acute respiratory distress syndrome), and known allergy to study medication.
Measures	After patient selection was made, participants were assigned a 1:1 ratio to either the intervention (Group D) or control (Group C) group using a random assignment in blocks of four. In Group D, dexmedetomidine infusion was started at 0.2–1.4 μg/kg/hr and titrated to achieve a target sedation of −2 to 0 on the Richmond Agitation Sedation Scale (RASS) and a CIWAA score of less than 15. In patients who did not achieve a −2 sedation score on the RASS or less than 15 on the CIWAA score, 10 mg of diazepam was administered according to a symptom-triggered protocol. In Group C, the same symptom-triggered diazepam regimen protocol was used. In both groups, diazepam was used every 30 minutes to control active withdrawal symptoms. In addition, haloperidol (5-mg IM boluses) was used as a rescue medication in both groups for severe agitation and hallucinations.
Findings	• Median 24-hour diazepam dose and median cumulative diazepam dose were lower in Group D.
	• Median percentage of time in the target sedation range was higher in Group D.
	• Fewer patients needed haloperidol in Group D.
	• Bradycardia was the only adverse effect in Group D.

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TABLE 1	Summary of Studies That Compared the Addition of Dexmedetomidine With Standard Benzodiazepine Therapy in the Treatment of AWS, Continued
Study	Crispo, A., Daley, M., Pepin, J., Harford, P., & Brown, C. (2014). Comparison of clinical outcomes in nonintubated patients with severe alcohol withdrawal syndrome treated with continuous-infusion sedatives: Dexmedetomidine versus benzodiazepines. *Pharmacotherapy, 34*(9), 910–917. doi:10.1002/phar.1448
Purpose	To compare efficacy and safety outcomes in nonintubated patients with severe alcohol withdrawal syndrome who require a continuous infusion of a benzodiazepine or dexmedetomidine in addition to standard medical therapy.
Sample	61 patients were included in the study. To be included, the patient had to have a diagnosis of alcohol withdrawal syndrome and be receiving a continuous infusion of either a benzodiazepine or dexmedetomidine and be between the ages of 18 and 89 years. The study was conducted between April 1, 2011, and October 31, 2012. Exclusions included intubation, history of seizure disorder, incomplete medical records, or an admission to the hospital in the last 30 days for alcohol withdrawal syndrome. The study was conducted in two different hospitals in Texas.
Measurements	A retrospective cohort study was performed. Patients were identified by cross matching a list of primary and secondary ICD diagnoses for alcohol withdrawal syndrome. The primary outcomes were analyzed by using the Fisher exact test. The two end points were respiratory distress requiring intubation or occurrence of alcohol withdrawal seizure. The other outcome measured was whether initiating dexmedetomidine decreased the amount of benzodiazepines patients needed during alcohol withdrawal.
Findings	• The dexmedetomidine group received a lower number of benzodiazepine doses after the initiation of the dexmedetomidine infusion.
	• Initiation of dexmedetomidine did not result in a lower number of intubations.
	• Dexmedetomidine was associated with more adverse effects such as hypotension and bradycardia
Study	Frazee, E., Personett, H., Leung, J., Nelson, S., Dierkhising, R., & Bauer, P. (2014). Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients. *Journal of Critical Care, 29*, 298–302. doi:10.1016/j.jcrc.2013.11.016
Purpose	To evaluate dexmedetomidine's impact on benzodiazepine requirements and hemodynamics in alcohol withdrawal syndrome.
Sample	33 patients were included in this retrospective case series. The study took place at the Mayo Clinic in Rochester, MN, between January 2006 and June 2012. Patients were included if they were at least 18 years old, were admitted to an ICU with a diagnosis of alcohol withdrawal syndrome, had received one dose of benzodiazepine before or on ICU admission, were started on dexmedetomidine, and received at least one CIWAA score within 24 hours of ICU admission. Patients were excluded if they did not authorize their medical record for review, developed alcohol withdrawal syndrome during workup for an alternate primary diagnosis, experienced a concurrent traumatic brain injury or intracranial hemorrhage, stayed in the ICU for less than 24 hours, were given clonidine in the 12 hours before or anytime during dexmedetomidine therapy, or resided in a correctional facility before admission.
Measurement	Benzodiazepine use was compared in the 12 hours before dexmedetomidine initiation and the 12 hours after initiation. Changes in heart rate, systolic blood pressure, and mean arterial pressure were evaluated after the initiation of dexmedetomidine. Data were collected from the electronic medical record because it was a retrospective case study.
Findings	• The use of benzodiazepines significantly decreased after starting the dexmedetomidine infusion.
	• Mean arterial pressure decreased after dexmedetomidine infusion was started.
	• Heart rate decreased after dexmedetomidine infusion was started.
	• Four patients experienced hypotension.
	• No patients experienced bradycardia.
Study	Ludtke, K., Stanly, K., Yount, N. L., & Gerkin, R. D. (2015). Retrospective review of critically ill patients experiencing alcohol withdrawal: Dexmedetomidine versus propofol and/or lorazepam continuous infusions. *Hospital Pharmacy, 50*(3), 208–213. doi:10.1310/hpj5003-208
Purpose	To evaluate sedation with a continuous infusion of dexmedetomidine versus propofol and/or lorazepam in critically ill patients experiencing alcohol withdrawal.

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TABLE 1	Summary of Studies That Compared the Addition of Dexmedetomidine With Standard Benzodiazepine Therapy in the Treatment of AWS, Continued
Sample	32 patients were included in the study. The study was a retrospective chart review done at the North Colorado Medical Center adult ICU between March 2002 and April 2009. Patients were included in the study if one of their first five diagnoses included alcohol withdrawal and they were treated with a continuous infusion of dexmedetomidine, propofol, or lorazepam. Patients were excluded if they were treated with a continuous infusion of both lorazapam and dexmedetomidine, propofol and dexmedetomidine, or a combination of all three drugs. Outcomes assessed were mechanical ventilation, length of mechanical ventilation, ICU length of stay, and hospital length of stay.
Measurements	A retrospective chart review was conducted. Numbers were analyzed by using the Mann–Whitney *U* test, Fisher's exact test, and linear regression. Outcomes assessed were mechanical ventilation, length of mechanical ventilation, ICU length of stay, and hospital length of stay.
Findings	• Patients being treated with dexmedetomidine were mechanically ventilated for a lesser time and had a lesser length of ICU and hospital stay when compared with patients being treated with propofol and lorazepam.
Study	Mueller, S. W., Preslaski, C. R., Kiser, T. H., Fish, D. N., Lavelle, J. C., Malkoski, S. P., & MacLaren, R. (2014). A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. *Critical Care Medicine, 42*, 1131–1139. doi:10.1097/CCM.0000000000000141
Purpose	To evaluate dexmedetomidine as an adjunctive therapy to lorazepam for severe alcohol withdrawal syndrome.
Sample	24 subjects who were admitted to the University of Colorado Hospital's medical ICU with severe AWS receiving standard therapy with a symptom-triggered AWS protocol were eligible for inclusion. Severe AWS was defined as CIWAA score of greater than or equal to 15 and the need for greater than or equal to 16 mg of lorazepam in a 4-hour period. Exclusion criteria included age less than 18 or greater than 85 years, administration of benzodiazepines for purposes other than AWS, current use of dexmedetomidine, patients not requiring ICU admission, administration of epidural medications, comatose patients by metabolic or neurologic affectation, active myocardial ischemia, second- or third-degree heart block, Child–Pugh Class C liver disease, pregnancy, or patients with known or suspected severe adverse reactions to dexmedetomidine.
Measurements	24 subjects were block randomized to receive either dexmedetomidine of 1.2 μg/kg/hr (high dose) or 0.4 μg/kg/hr (low dose) or placebo as an adjunctive therapy to the standard of care of the AWS protocol. Primary outcomes measured were the change in total lorazepam requirements over the 24-hour period after starting the study drug compared with the 24-hour period before starting the study drug and cumulative lorazepam doses over the first 7 hospital days of AWS. Secondary outcomes measured included total and daily lorazepam requirements after starting the study drug and endotracheal intubation.
Findings	• There was no significant difference in lorazepam requirements 24 hours before starting the study drug.
	• Median lorazepam requirements 24 hours after starting the study drug were numerically different but not statistically lower in the treatment arm.
	• The difference between the 24-hour lorazepam requirements before starting the study drug compared with 24-hour after the study drug was significantly lower with dexmedetomidine compared with the placebo.
	• Median lorazepam requirements over the first 7 days of hospitalization were not statistically different between the dexmedetomidine and placebo arms.
	• ICU and hospital lengths of stay were similar in all treatment arms.
	• Adverse effects of dexmedetomidine experienced were bradycardia and hypotension.
Study	Muzyk, A. J., Kerns, S., Brudney, S., & Gagliardi, J. P. (2013). Dexmedetomidine for the treatment of alcohol withdrawal syndrome: Rationale and current status of research. *CNS Drugs, 27*(11), 913–920. doi:10.1007/s40263-013-0106-6
Purpose	To evaluate whether the addition of dexmedetomidine therapy in conjunction with standard benzodiazepine therapy, in the treatment of AWS, would decrease hospital length of stay and benzodiazepine requirements.
Sample	A retrospective review was conducted in two intervals. Interval 1 included patients admitted to Maricopa Integrated Health System's ICU with a primary or secondary diagnosis of AWS between January 2005 and September 2007. Interval 1 was treated with benzodiazepine monotherapy only. Interval 2 consisted of patients with the same diagnosis at the same hospital, who were admitted between January 2010 and December 2010. Interval 2 patients were treated with an adjunctive therapy such as dexmedetomidine, in addition to the standard benzodiazepine therapy.

(continues)

TABLE 1	Summary of Studies That Compared the Addition of Dexmedetomidine With Standard Benzodiazepine Therapy in the Treatment of AWS, Continued	
Measurements		Interval 1 included 87 patients, and interval 2 included 54 patients. Benzodiazepine basal dose, hospital length of stay, and ICU length of stay were compared.
Findings		• Patients receiving dexmedetomidine required a lower benzodiazepine basal dose.
		• ICU and hospital lengths of stay were not altered by adjunctive therapy.
		• Adverse effects of dexmedetomidine experienced were bradycardia and hypotension.

Similarly, Frazee et al. (2014) performed a retrospective case series that evaluated 33 critically ill adults with an admission diagnosis of AWS being treated with dexmedetomidine. The purpose of their study was to evaluate dexmedetomidine's impact on benzodiazepine requirements and hemodynamic in the treatment of AWS. Initiation of a dexmedetomidine infusion leads to a significant reduction in the amount of benzodiazepine use, with a median reduction of 20 mg within 12 hours of beginning the infusion (Frazee et al., 2014). Three patients experienced a 100-mg reduction in lorazepam requirement, and five patients received no further benzodiazepines after the introduction of dexmedetomidine (Frazee et al., 2014). In terms of the effect of dexmedetomidine on hemodynamics, 12% of the participants developed hypotension. Conversely, there were no incidences of bradycardia (Frazee et al., 2014).

Puscas et al. (2016) performed a single-site retrospective observational study that compared the use of benzodiazepines as a monotherapy to treat AWS with the use of adjunctive therapies, such as dexmedetomidine. Patient records for two intervals were reviewed. Interval 1 included 87 patients admitted to the ICU with a diagnosis of AWS for which benzodiazepine monotherapy was utilized. Interval 2 included 54 patients admitted to the ICU with a diagnosis of AWS who were treated with adjunctive agents in addition to benzodiazepines, including propofol and dexmedetomidine. The use of a dexmedetomidine infusion was associated with a decreased level of benzodiazepine basal dose needed (84 vs. 101 mg; Puscas et al., 2016). In addition, Puscas et al. found no statistical difference in length of either ICU (Interval 1 = 2.8 days vs. Interval 2 = 5.3 days) or hospital stay (Interval 1 = 8.1 days vs. Interval 2 = 9.3 days) in those treated with dexmedetomidine. Harmful side effects of dexmedetomidine were also evaluated. Six of the 31 patients receiving dexmedetomidine required a reduction in the rate of the infusion due to bradycardia and/or hypotension. In addition, two participants required discontinuation of the drug because of bradycardia and hypotension (Puscas et al., 2016).

Beg et al. (2016) performed a retrospective cohort study that included 77 patients and evaluated the difference in lorazepam equivalents in the 24 hours before and after the addition of dexmedetomidine therapy. The overall benzodiazepine use was lower with the addition of dexmedetomidine (21 mg before initiation vs. 11 mg 24 hours after initiation), but it was not statistically significant ($p = .10$; Beg et al., 2016). In contrast to other studies, Beg et al. found that the hospital (monotherapy = 4.7 days vs. combination therapy = 8.9 days) and ICU (monotherapy = 1.4 days vs. combination therapy = 2.9 days) lengths of stay were longer in those treated with a combination therapy. In addition, four patients in the combination therapy group had to discontinue dexmedetomidine because of hypotension and/or bradycardia (Beg et al., 2016).

Similar to Beg et al. (2016), Mueller et al. (2014) performed a randomized, double-blind, placebo-controlled study that compared lorazepam requirements 24 hours and 7 days after the initiation of a dexmedetomidine infusion. Lorazepam requirement was reduced (−56 vs. −8 mg) in the 24 hours after the initiation of a dexmedetomidine infusion. However, the use of lorazepam 7 days after the initiation of a dexmedetomidine infusion was numerically lower (159 vs. 181 mg) but not statistically significant ($p = .23$; Mueller et al., 2014). In addition, the median ICU stay in those treated with dexmedetomidine was 4.7 days, and that in those treated with benzodiazepines was only 4 days. In addition, the comparison of length of hospital stay was similar as well (benzodiazepine group = 7.4 days vs. dexmedetomidine group = 10 days; Mueller et al., 2014). Similar to other studies, participants who received dexmedetomidine also experienced bradycardia (four patients) and hypotension (three patients; Mueller et al., 2014).

Bielka et al. (2015) performed a randomized, single-center, control study on 72 participants, which compared the benzodiazepine consumption use between two groups. Participants were randomly assigned to either Group 1 or Group 2. Group 1 was started on a dexmedetomidine infusion in addition to a symptom-triggered benzodiazepine protocol. Group 2 was only treated with the symptom-triggered benzodiazepine protocol. The median 24-hour benzodiazepine consumption (Group 1 = 20 mg vs. Group 2 = 40 mg) and median cumulative benzodiazepine dose during the ICU stay (Group 1 = 60 mg vs. Group 2 = 90 mg) were significantly lower in Group 1 (Bielka et al., 2015). The study also evaluated the length of ICU stay. The median ICU stay was approximately 50 hours in patients who were treated with dexmedetomidine in conjunction with benzodiazepines. Conversely, patients who were only treated with a benzodiazepine had an ICU stay of

approximately 70 hours (Bielka et al., 2015). Similar to other studies, Bielka et al. found that eight of 35 participants in the dexmedetomidine group experienced hypotension and 10 of the 35 participants developed bradycardia.

Ludtke, Stanley, Yount, and Gerkin (2015) performed a retrospective chart review on ICU admissions for AWS in which 32 patients were treated with either a continuous infusion of dexmedetomidine, propofol, or lorazepam. The purpose of their review was to evaluate whether dexmedetomidine therapy reduced the incidence of intubation. Of the patients in the dexmedetomidine group, only two required intubation. In contrast, of the patients treated with propofol or lorazepam, 10 required intubation (Ludtke et al., 2015). ICU and hospital lengths of stay were also explored. Patients treated with a continuous infusion of dexmedetomidine had an ICU stay of about 53 hours, whereas those treated with a continuous infusion of a benzodiazepine had an ICU length of stay of approximately 114.9 hours. In addition, hospital length of stay was less in the dexmedetomidine group, 135.8 hours, versus the benzodiazepine group, 241.1 hours (Ludtke et al., 2015).

DISCUSSION

This review explored the addition of dexmedetomidine therapy to the standard therapy in treating AWS. The seven studies included in this review suggest that dexmedetomidine is a potentially safe and effective adjunctive treatment for patients diagnosed with AWS in the ICU. Dexmedetomidine therapy is beneficial to those patients who require escalating doses of benzodiazepines or who are refractory to benzodiazepine therapy. Increased benzodiazepine doses can lead to oversedation and an increased risk of respiratory distress and intubation. Dexmedetomidine has no effect on the GABA receptors and produces sedative and anxiolytic effects without respiratory compromise. Dexmedetomidine should not be used as a monotherapy because it has no antiepileptic properties.

Several studies included in this review showed that the addition of dexmedetomidine therapy reduced the amount of benzodiazepines needed. Crispo et al. (2014) found that the addition of a dexmedetomidine infusion in conjunction with the standard treatment of AWS leads to a decrease in the median "as needed" benzodiazepine doses. Similarly, Frazee et al. (2014) found that, within 12 hours of initiating a dexmedetomidine infusion, the median amount of benzodiazepine doses was reduced. Both Puscas et al. (2016) and Bielka et al. (2015) compared benzodiazepine consumption between groups utilizing monotherapy versus combination therapy. Combination therapy included the use of a dexmedetomidine infusion. Both Puscas et al. and Bielka et al. found that the addition of a dexmedetomidine infusion decreased the total amount of additional benzodiazepine doses needed to treat AWS. Mueller et al. (2014) and Beg et al. (2016) both compared the amount of benzodiazepine use 24 hours after the initiation of a dexmedetomidine infusion. Both Mueller et al. and Beg et al. found that the addition of a dexmedetomidine infusion decreased the amount of benzodiazepines needed to control the symptoms of AWS. However, although Beg et al. found that the dose of benzodiazepine was numerically lower, it was not statistically significant. On the basis of these studies, it can be concluded that the initiation of a dexmedetomidine infusion reduces the amount of benzodiazepines needed to control the symptoms of AWS.

Two studies in this review evaluated the incidence of respiratory distress requiring intubation. Crispo et al. (2014) hypothesized that the addition of dexmedetomidine therapy would reduce the number of incidences of respiratory distress requiring intubation. Although the occurrence of respiratory distress requiring intubation was lower in the dexmedetomidine group, it was not statistically significant (Crispo et al., 2014). Ludtke et al. (2015) found that the addition of a dexmedetomidine infusion decreased the intubation rate. Therefore, because only two studies were included in this review and the results are conflicting, more studies focused on this topic need to be completed.

The addition of dexmedetomidine in the treatment of AWS could potentially reduce the length of ICU and hospital stay. Because the use of dexmedetomidine may reduce the amount of benzodiazepines needed to treat AWS, the length of time it takes for AWS to resolve should decrease. Bielka et al. (2015) and Ludtke et al. (2015) both found that the addition of a dexmedetomidine infusion decreased the length of ICU stay. In addition, Ludtke et al. found that the length of hospital stay was also lower in those patients treated with dexmedetomidine. In contrast, Mueller et al. (2014) and Puscas et al. (2016) concluded that there was no difference in the length of ICU or hospital stay in those treated with dexmedetomidine. In addition, Crispo et al. (2014) also found no significant difference in the length of hospital stay. Conversely, Beg et al. (2016) found that those treated with dexmedetomidine had an increase in both hospital and ICU lengths of stay. The results of the studies included in this review provide conflicting evidence as to whether the addition of dexmedetomidine has an effect on ICU or hospital length of stay.

Dexmedetomidine is associated with severe side effects including hypotension and bradycardia. Of the seven studies included in this review, participants in five studies experienced either hypotension and/or bradycardia. Some participants of Puscas et al. (2016), Mueller et al. (2014), Crispo et al. (2014), and Bielka et al. (2015) experienced hypotension and/or bradycardia. Discontinuation of the dexmedetomidine infusion due to hypotension and/or bradycardia occurred in at least one study. In contrast, participants in Frazee et al. (2014) experienced hypotension, but not bradycardia. The addition of dexmedetomidine may be beneficial in reducing the amount of benzodiazepines needed to control the symptoms of AWS, but it should be used cautiously because of its adverse side effects. Patients who are receiving a dexmedetomidine infusion should be closely monitored in the ICU.

CONCLUSION

The literature argues that the addition of dexmedetomidine therapy, in the treatment of AWS, may lower the total amount of "as needed" benzodiazepine doses to control symptoms.

Lowering the total dose of benzodiazepine is beneficial to the patient for numerous reasons including the reduced rate of oversedation leading to respiratory distress and intubation. However, outcomes regarding the reduced incidence of intubation are conflicting, and more studies focused on this need to be performed. In addition, results regarding the reduction in the length of ICU and hospital stay are conflicting, and more studies need to be completed. Dexmedetomidine has potential severe side effects such as hypotension and bradycardia, which need to be taken into consideration. Although the addition of dexmedetomidine therapy lowers the total amount of benzodiazepines needed to treat AWS, more studies need to be completed to confirm its safety and efficacy.

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