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Original Article

Clonidine as early adjunctive therapy for alcohol withdrawal in the emergency department

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Abstract. Alpha-2-agonists may decrease cumulative benzodiazepines (BZD) requirements in alcohol withdrawal syndrome (AWS), leading to a reduction in BZD related adverse events. This study aimed to evaluate the impact of adjunctive clonidine on BZD requirements in patients with AWS who presented to the emergency department (ED). A retrospective chart review study from 1/2015 to 12/2016 was performed in patients who were admitted for AWS via the ED and would have received at least 24 hours of benzodiazepines. The primary study outcome was the difference of the 12-hour cumulative BZD requirements in lorazepam equivalents (BZD-LE) in patients who received clonidine compared to patients who received BZD monotherapy. Secondary endpoints included total hospital benzodiazepine requirements, intensive care unit (ICU) admission, ICU and hospital length of stay, and incidence of hypotension. A total of 11 patients who received clonidine adjunctive therapy and 33 patients to standard management were included in the study. The median 12 hour cumulative BZD-LE was 16 mg (IQR 3-19) in the intervention group compared to 7 mg (IQR 4-13) in the control group (P = 0.90). However, the total cumulative BZD-LE requirements for the hospital stay was 31 mg (IQR 21-48) in the intervention group compared to 45 mg (IQR 26-71) in the control group (P = 0.28). In conclusion, adjunctive clonidine administration to BZD in AWS initiated in the ED was not associated with a decrease in 12 hour BZD requirements.

Keywords: Alcohol withdrawal, clonidine, adjunctive therapy

Introduction

Alcohol use disorders remains a significant burden to the healthcare system with an annual estimated 1.2 million hospital admissions related to alcohol abuse [1]. Of those 500,000 episodes experience severe withdrawal symptoms that necessitate inpatient treatment.

Prolonged alcohol abuse leads to the development of physical dependence in which the brain undergoes changes to maintain neurotransmitter homeostasis [2]. As a result patients that abruptly cease alcohol consumption experience autonomic hyperactivity of the central nervous system (CNS) [2]. Thus, symptoms of alcohol withdrawal syndrome (AWS) results from an excessive sympathetic surge in the acute absence of alcohol [1, 3, 4]. Depending on the severity of AWS, symptoms may be mild such as mild tremors, tachycardia, hypertension or in the case of severe untreated AWS exhibiting severe agitation, seizures, hallucinations, and delirium tremens which if left untreated is fatal [1, 5]. Benzodiazepines (BZDs) are the treatment of choice in AWS.

Although BZDs have been used for decades, there is no studies to indicate the ideal BZD nor treatment strategy in the management of AWS(1). In an effort to avert AWS, clinicians may be aggressive with BZD dosing which may inadvertently cause respiratory depression necessitating mechanical ventilation and an intensive care unit (ICU) admission.

Thus, there is a renewed interest in agents that may be used adjunctively with BZD for the treatment of early AWS. Centrally acting pre-synaptic α-2 receptor agonists such as clonidine and dexmedetomidine are examples of such adjunctive agents that may be utilized in the management of AWS. We sought to investigate the impact of early adjunctive clonidine on BZDs requirements in early AWS patients who presented to the ED compared to standard management.

Materials and Methods

This was a retrospective study conducted at a tertiary care center of patients 18 years of age and older who presented to the Emergency Department (ED) and were admitted inpatient with the primary diagnosis of AWS from January 2015 to December 2016. Patients were identified using ICD 9 (291.81) and ICD 10 (F10.231 & F10.231) billing codes. Inclusion criteria were patients admitted for AWS, receiving at least 24 hours of BZDs (T=0 defined as time from first BZD administration in the ED) and the use of clonidine as adjunctive therapy for the

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TABLE 1
LORAZEPAM EQIVALENTS

1 mg oral lorazepam
0.25 mg oral clonazepam
0.5 mg oral alprazolam
0.5 mg intravenous lorazepam
5 mg intravenous diazepam
10 mg oral chlordiazepoxide

treatment of AWS. Trauma and or intubated patients, the administration of any other neuromodulating agents (i.e: gabapentin, valproic acid, ketamine, carbamazepine, guanfacine) other than BZDs, the administration of clonidine as part of an antihypertensive regimen, patients discharged directly from the ED and patients whom primary diagnosis is other than alcohol withdrawal were excluded from analysis.

The primary outcome was defined as the difference in the 12-hour cumulative BZDs requirements in patients who have received adjunctive clonidine (AC), compared to patients who received standard BZDs monotherapy for the management of their AWS (SM). Secondary endpoints were defined as the difference in the 24 hour cumulative BZD requirement, total administered BZDs requirements during the hospital stay, ICU admission, ICU and hospital length of stay, rates of respiratory depression and the incidence of hypotension (defined as systolic blood pressure less than 90 mmHg). All benzodiazepines doses were converted to and reported as lorazepam equivalents (BZD-LE) (Table 1) [6, 7]. All tests were two-tailed with alpha set at $p < 0.05$. Continuous data was analyzed using a T-test. Categorical data was analyzed using Chi-squared test. All statistical analysis was performed using IBM SPSS.

Results

A total of 18 patients were screened for inclusion in the AC group. Six patients were discharged from the ED and were excluded from further analysis. One patient's primary diagnosis was not alcohol withdrawal and was excluded. A total of 11 patients were included in the clonidine group for analysis. A total of 42 patients were screened for inclusion in the SM group. Nine patients were excluded for receiving adjunctive therapy other than clonidine for the management of their AWS. The remainder 33 patients were included into the SM group. Baseline characteristics were similar between the two groups (Table 2). Overall, the majority of patients presenting with AWS were men with median systolic blood pressure (SBP) and median heart rate (HR) of 185 mmHg and 132 bpm in the clonidine group compared to the standard management group's median SBP of 167 and median HR of 120 bpm. Serum ethanol levels ranged from undetectable up to 430 mg/dl (median: 29 mg/dl) in the AC group, and from undetectable to 427 mg/dl (median: 101 mg/dl) in the SM group.

TABLE 2
BASELINE CHARACTERISTICS

	Intervention group (n=11)	Control group (n=33)
Age	50 (38-52)	47 (40-54)
Sex, male (n, %)	9 (82)	28 (85)
Weight (kg)	73 (67-78)	77 (69-89)
Maximum SBP (mmHg)	185 (143-206)	167 (146-194)
Maximum DBP (mmHg)	101 (92-119)	99 (81-109)
Maximum HR (BP)	132 (112-138)	120 (107-130)

Results reported in median (IQR) unless otherwise noted.

The median cumulative dose of clonidine administered in the ED was 100 mcg and ranged between 100 mcg and 300 mcg. The median time to clonidine administration was 4 hours, while the median ED stay was 6 hours. Clonidine therapy was continued during inpatient therapy in 10 out of 11 patients (91%). As there was no standardized protocol, the resumption of clonidine was left to the discretion of the admitting team in the inpatient service with the majority of patients receiving 100mcg three times daily. The median duration of clonidine therapy was 3 days and ranged from 1 to 4 days.

The median 12 hour cumulative BZD-LE requirement was 16 mg (IQR 3-19) in the AC compared to 7 mg (IQR 4-13) in the SM group $P = 0.90$. At 24 hours, the median cumulative BZD-LE requirement was 21 mg (IQR 16-30) in the AC group and 18 mg (IQR 11-34) in the SM group $P = 0.44$. The median total cumulative BZD-LE requirement was 31 mg (IQR 21-48) in the AC group compared to 45 mg (IQR 26-71 mg) in the SM group $P = 0.28$.

At 12 hours, the median BZD-LE requirements in the AC group were 9 mg higher compared to the SM group, that difference however decreased at the 24 hour mark where the AC group required higher total requirement of 3 mg compared to the SM group. Upon patient discharge, the median total cumulative BZD-LE dose was 14mg higher in the SM group compared to the AC group (Table 3 and Fig. 1).

The rate of ICU admission was not different between the AC group (45%) and the SM group, (42%). Neither the median ICU days nor the median hospital days was different between the two groups AC group 2 days (IQR 2-3), 4 days (IQR 3-5), SM group, 2 days (IQR 2-5), 4 days(IQR 4-8) respectively. Three patients experienced hypotension in the SM group (9%), and none in the AC group, however that was not statistically significant (Table 4). There was no reported respiratory depression necessitating intervention and or intubation.

Discussion

At our institution there is no standardized approach regarding the management of AWS. Choice, route and frequency of BZD is left up to the discretion of the provider. The treatment approach is then dictated via patient presentation, alcohol blood level and patient vitals. The use of adjunctive therapies are thus optional and varies between medical and pharmacy providers. GABA agonism

TABLE 3
BASELINE CHARACTERISTICS

	Intervention group (n=11)	Control group (n=33)	P-Value
12 hrs cumulative BZD (mg)	16 (3-19)	7 (4-13)	0.9
24 hrs cumulative BZD (mg)	21 (16-30)	18 (11-34)	0.44
Total cumulative BZD (mg)	31 (21-48)	45 (26-71)	0.28

Results reported as milligrams of lorazepam equivalents in median (IQR).

TABLE 4
SECONDARY ENDPOINTS

	Intervention group (n=11)	Control group (n=33)
ICU admission (n, %)	5 (45)	14 (42)
ICU Length of stay (days)	2 (2-3)	2 (2-5)
Hospital length of stay (days)	4 (3-5)	4 (4-8)
Hypotension (n, %)	0 (0)	3 (9)

Results reported as median (IQR) unless otherwise noted.

remains the only treatment for AWS, however, historically providers use the minimum effective dose required for concerns of ADE. Thus, we sought to investigate if the use of early clonidine administration may translate to reduced BZD requirements.

Our results indicate that the use of clonidine as adjunctive therapy in early AWS did not reduce 12 hour BZD requirements compared to patients receiving standard management. However, at 24 hours and at time of discharge, patients receiving clonidine adjunctive therapy required less BZD compared to patients that did not receive clonidine.

It has been well established that the neurotransmitter effects of chronic ethanol use leads to a decrease in γ-aminobutyric acid subtype-A (GABAa) receptor functioning. Subsequently, an increase in effort to adapt to the increased inhibitory $GABA_A$ stimulation, glutamate, NMDA receptors are upregulated [8]. The downregulation of $GABA_A$ receptors is compounded by the change of the change of the GABA receptor subunit that is available for activation, making them less responsive to synaptic neurotransmitters. Norepinephrine and dopaminergic levels have been shown to be elevated with chronic ethanol intake and the dysregulation of the neurotransmitters explains the sympathetic surge witnessed in AWS [9].

Upon abrupt cessation of ethanol intake, the unopposed increased N-methyl-D-asparte (NMDA) receptor activity coupled with the downregulated, less sensitive $GABA_A$ receptors places the patient at a high risk for AWS [8]. Excessive dopamine, and norepinephrine levels unopposed by alcohol cessation have been demonstrated in AWS [10]. Pre-synaptic neuron releases catecholamines such as norepinephrine and dopamine resulting in the over activation of the sympathetic nervous system, leading to an increased anxiety, tremors and sympathetic tone exhibited by hypertension and tachycardia [10].

Individuals that chronically intake ethanol are at a higher risk for AWS, as ethanol is highly specific to the $GABA_A$ receptors, inducing a higher tolerance [6, 7]. Thus these patients generally may require higher doses of BZD for AWS symptom control [7]. Although BZD are the treatment of choice for symptom management of AWS, there has not been any evidence to suggest superiority of one BZD over the other [1, 11-13]. Rapid escalation of doses may be required in the refractory patient, however adverse effects such as respiratory depression and sedation necessitating intubation may occur, though rare. Adjunctive therapy may be of interest in the setting of severe alcohol withdrawal to mitigate the use of high dose BZDs.

Thus, there has been a renewed interest in the use of adjunctive therapy in AWS patients, in an effort to reduce the total amount of BZD. The addition of such agents may blunt the sympathetic response to AWS by decreasing the norepinephrine and epinephrine levels during AWS, leading to an overall BZDs sparing effect [1, 14-16]. Agents such as dexmedetomidine, clonidine, carbamazepine and valproic acid have all been studied in this setting [17-19]. Aside from one study that compared gabapentin to lorazepam for the treatment of mild to moderate AWS, the treatment of choice of AWS remains to be BZDs [20, 21].

Clonidine, approved in 1974 is the oldest central alpha 2 agonist, via creating a negative feedback loop and binding to the pre-synaptic neuron decreases the release of catecholamines. This unique mechanism of action is how clonidine may be of benefit in the body's pro-excitatory state in the setting of AWS [22, 23]. Thus, there is a proposed benefit to add clonidine in patients presenting with hypertension, tachycardia anxiousness, agitation, diaphoresis, and requiring aggressive doses of BZDs [1, 7].

The first reported study for the use of adjunctive clonidine in AWS patients, admitted in a non-ICU setting was published in 1975 by Bjorkqvist. The author compared the use of clonidine vs. placebo in patients receiving standard care for AWS and evaluated a "Nurses Evaluation Score" which graded the patient's general condition, sleep disturbance, movements and behavior for each patient. Additionally, patient vitals, and tremor severity was recorded. The clonidine dose was 0.15mg, and was given as TID with a rapid taper over 4 days. The use of clonidine was associated with a lower Nurses Evaluation Score by day 2 ($P<0.01$), less tremulous and less incidence of hypotension compared to the placebo group [13]. There was no difference in the incidence of adverse drug reactions. The author highlighted that clonidine should not be the sole therapy for AWS, rather "a useful aid" in AWS. Walinder et al. investigated clonidine compared to standard care (BZD) in 26 patients, in a randomized open label study in 1981 [24]. This non-ICU study demonstrated equal efficacy of clonidine compared to BZD with no difference in side effects. Limitations to this study included using a different scoring system and patients receiving clonidine had a higher alcohol use prior to study initiation [24].

A subsequent study in 1985 by Manhem et al. sought out to compare clonidine (0.15mg-0.3mg every 6 hours) to

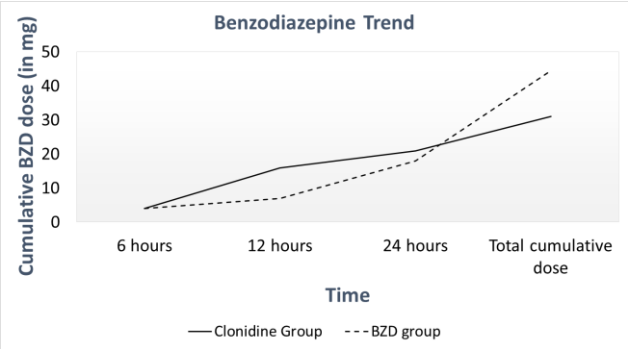

Figure 1 Cumulative benzodiazepine trend.

chlormethiazole (a non-BZD hypnotic that has been used for the management of AWS) in 20, non-ICU AWS patients [25]. The authors investigated the effect of therapies on blood pressure, an alcohol withdrawal assessment scale. Seventeen patients who completed the study, the use of standard treatment and clonidine was associated with a significant decrease in lowering systolic blood pressure, heart rate and the alcohol withdrawal assessment scale compared to standard treatment. The authors drew plasma norepinephrine and epinephrine levels and compared it between clonidine and non-clonidine recipients. Patients' norepinephrine and epinephrine levels who received clonidine were lower compared to non-clonidine patients ($P<0.01$), and proved the basis for clonidine's potential for use in AWS. Two subsequent studies by Baumgartner et al and Robinson et al were conducted, both concluded that the use of clonidine as adjunctive to standard treatment was associated with lower alcohol withdrawal syndromes, systolic blood pressure and heart rate [26, 27]. None of these studies initiated the use of clonidine in the emergency department.

With the introduction of dexmedetomidine, a highly selective intravenous alpha-2 agonist, the use of adjunctive modalities for the treatment of AWS was reignited. A randomized prospective double blind, placebo controlled study by Mueller et al compared patients treated for AWS with lorazepam with or without dexmedetomidine [28]. The primary efficacy outcome was the change in total lorazepam requirements 24 hours prior to and 7 days preceding the initiation of the intervention while the primary safety outcome was rates of hemodynamic instability (bradycardia and or hypotension). Patients initiated on dexmedetomidine required less lorazepam in the first 24 hours ($P = 0.037$) compared to placebo, but at 7 days, they difference was not statistically different. Bradycardia unsurprisingly was much more common in the dexmedetomidine group compared to placebo.

VanderWeide et al. conducted a retrospective, cohort study evaluating the impact of adjunctive dexmedetomidine on BZD us in the critically ill patients presenting with AWS. Patients either received dexmedetomidine plus standard alcohol withdrawal protocol versus the institutions standard alcohol withdrawal protocol. The authors found that adjunctive dexmedetomidine demonstrated a BZD sparing effect as compared to the standard alcohol withdrawal protocol, however failed to demonstrate an impact on clinical outcomes such as incidence or duration of mechanical ventilation and length of ICU or hospital stay [22].

Although beneficial as adjunctive therapy in AWS, alpha 1 agonists should *not* be used as monotherapy. This was demonstrated in a study by Robinson et al, where clonidine monotherapy was associated with higher rates of hypotension and lack of efficacy [26]. Adinoff et al. compared clonidine vs diazepam vs alprazolam vs placebo for alcohol withdrawal, and found that clonidine monotherapy was essentially as effective as placebo [29].

We sought to evaluate the impact of adjunctive clonidine on BZD requirements in patients with AWS who presented to the ED, and if suppressing the catecholamine surge in the ED may confer clinical and disposition benefits (i.e., ICU vs non-ICU admission, excessive lethargy). Currently at our institution, there is no standard of care regarding the management of AWS. Choice, route and frequency of BZD is left up to the discretion of the provider, in which presentation, alcohol blood level and patient vitals plays a role in the approach and management of these patients. The use of adjunctive therapies are optional and varies between medical and pharmacy providers.

This is different than most studies in which patients were initiated on adjunctive therapy upon admission or due increasing BZD requirements [25]. We hypothesized that the use of early clonidine would have decreased the total amount of BZD use early in the management of AWS. Our results demonstrated that the AC group had higher BZD requirements early on AWS management compared to the SM group at 12 hours, although by the end of the hospital stay the SM group ultimately required more BZDs. The higher BZD requirements may be due to these patient experiencing more severe AWS early in the hospital stay increasing the 12 hour cumulative BZD doses. There may also be some component of a "therapy delay effect" defined as time delta from ED admission with AWS to clonidine administration which was 4 hours in our study. Therapy delay effect may extend further depending on the onset of action and up titration depending to response and tolerability. This hypothesis would account for the trend observed in that the intervention group ultimately requiring less cumulative BZD use than the control group despite the higher 12 hour requirements.

Although statistically non-significant difference in the BZD requirements, there was an overall trend of increasing BZD in the SM group vs. AC group by the end of the hospitalization (Table 3). Additionally, the rate of clonidine continuation was higher than expected highlighting the potential role of clonidine therapy as adjunctive in AWS.

Our study had several limitations. First, due to the small sample size, the study was not powered to detect a statistical difference. Second, our institution does not have a standardized approach regarding the use of BZD and adjunctive therapy in AWS, thus clonidine may have been preferentially used in patients with more severe AWS. Thirdly, due to limitations with the electronic medical record at the time, the documentation of CIWAs were

lacking and rarely documented, making a direct AWS comparison challenging. There is a possibility that patients with more severe AWS led to the selection for the use of clonidine in these patients. Thus selection bias for the administration of clonidine to severe AWS compared to mild or moderate AWS is a possibility. Lastly, the discretion to initiate clonidine therapy was determined by the bedside physician as there was no institutional protocol. This study did not attempt to differentiate the efficacy of once clonidine dose from another, and although there studies had clonidine doses starting with 150mcg up to 300mcg, 100mcg is a reasonable starting dose which may be repeated to target response based on the practitioner's assessment [16].

Conclusion

Adjunctive clonidine administration to BZD in AWS in the ED was not associated with a decrease in 12 hour BZD requirements, ICU admission, or ICU or hospital days. Clonidine was safe and well-tolerated, larger prospective studies are needed to further evaluate the use of adjunctive clonidine in the ED for AWS management.

Conflict of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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