CLINICAL INVESTIGATION

Outcomes of Minnesota Detoxification Scale (MINDS) Assessment With High-dose Front Loading Diazepam Treatment for Alcohol Withdrawal in Hospitalized Patients

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ABSTRACT

Background: Benzodiazepines are the gold standard for alcohol withdrawal treatment but choice and dosing vary widely. In 2015, our institution implemented a Minnesota detoxification scale (MINDS) and single standardized high-dose diazepam based protocol for treatment of alcohol withdrawal to replace multiple Clinical Institute Withdrawal Assessment for Alcohol (CIWA) based protocols using lower dose benzodiazepines. We compared use of MINDS versus CIWA assessment protocols with high front loading diazepam treatment in care of patient experiencing alcohol withdrawal during hospitalization.

Methods: Retrospective cohort study of hospitalized patients experiencing alcohol withdrawal to statistically analyze difference in outcomes between CIWA based lower benzodiazepine dose protocols used in 2013–2015 versus the MINDS based high-dose front-loading diazepam protocol used in 2015–2017.

Results: Patients treated with MINDS based high dose diazepam protocol were less likely to have physical restraints used (AOR = 0.8, CI: 0.70–0.92), had a shorter hospital length of stay, and fewer days on benzodiazepines ($p < 0.001$). Patients were more likely to be readmitted to the hospital within 30 days (AOR = 1.13, CI: 1.03–1.26) in MINDS based diazepam treatment group. Total diazepam equivalent dosing was similar in both groups. Mortality rates and ICU use rates were similar between the groups.

Conclusions: Higher dose front loading long acting benzodiazepine can be safely used with beneficial outcomes in hospitalized alcohol withdrawal patients.

Keywords: Alcohol withdrawal; Benzodiazepines; MINDS; Hospitalization; Physical restraints. **[Am J Med Sci 2021;■(■):1–6.]**

INTRODUCTION

The costs associated with alcohol use disorder amount to more than 1% of the gross national product in high-income and middle-income countries.[1] At some point in their lives 20% of men and 10% of women in most western societies will have an alcohol-use disorder. Half of patients with alcohol-use disorder will experience withdrawal symptoms after decreased alcohol consumption and about 3–5% of patients have seizures and delirium tremens.[2,3] Alcohol withdrawal is a common cause of admission to a hospital and into the intensive care unit (ICU).[4] Patients experiencing alcohol withdrawal often place themselves at increased risk of self-harm and harm to staff involved in their care. Physical restraints are commonly used for patients undergoing significant withdrawal reactions and can be psychologically traumatic for patients and family members alike.

Benzodiazepines are the gold standard for treatment of alcohol withdrawal.[5,6] Studies have indicated symptom triggered therapy rather than fixed dose scheduled benzodiazepines is safe, effective, and is associated with a decrease in quantity of medications administered and duration of treatment.[7] Although other medications including gabapentin, baclofen, and carbamazepine

have been suggested for use in management of symptoms of alcohol withdrawal, currently benzodiazepines are considered the cornerstone of treatment.[8–10]

Several different rating scales have been described for assessment of alcohol withdrawal.[11] The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) was described with 15 items.[12] A revised version of this scale, CIWA-Ar with 10 items, was described later with increased efficiency while simultaneously retaining clinical usefulness, validity, and reliability.[13] The Minnesota detoxification scale (MINDS) is less studied but is an effective assessment tool, especially in ICU patients who are sicker and for whom subjective symptoms are difficult to assess (e.g. anxiety). One study indicated that for ICU patients with alcohol withdrawal disorder, use of a symptom-driven protocol significantly decreased the time required for symptom control, amount of sedative required, and the amount of time spent receiving an infusion compared to a non-protocol approach.[14]

The choice and dosing of benzodiazepines for alcohol withdrawal treatment vary widely. Although lorazepam is preferred by many, others have argued strongly in favor of diazepam due to it's shorter time to peak effect that allows for rapid symptom control and release of long-acting metabolites that provide a smooth withdrawal.[15,16] Some studies have found that high dose benzodiazepines with deferred intubation is safe in severe withdrawal patients in the ICU.[17]

At an 11-hospital system located in Minnesota and Western Wisconsin, multiple alcohol withdrawal treatment protocols mostly with CIWA-Ar assessment tool and lower dose benzodiazepine were in use before 2015. Assessment with the MINDS scale and a single standardized high dose front loading diazepam based treatment protocol (loading dose up to 80 mg diazepam) with the MINDS assessment tool was implemented beginning in 2015 for treatment of patients who experience alcohol withdrawal during hospitalization.

The goal of implementation of the MINDS protocol was to improve patient outcomes using a front-loading approach with longer acting benzodiazepines and at the same time standardize care of patients who experience alcohol withdrawal during hospitalization. The MINDS based protocol was developed by a panel of health care providers including hospitalists, intensivists, psychiatrists, and registered nurses (RNs) at our institution. Once a standardized protocol was designed, it was trialed at one hospital site for its effectiveness and safety in a small set of patients against treatment protocols being used at the time. A dashboard was also created for the following three years and critical events were reviewed by the workgroup.

The purpose of this study was to compare outcomes in hospitalized patients who experience alcohol withdrawal who were treated with use of the MINDS assessment protocol using high-dose long acting benzodiazepines versus previous CIWA based assessments with lower dose short acting benzodiazepines.

METHODS

Study design

We evaluated patients' data collected from January 2013 to December 2017 using a retrospective cohort based comparative approach at an 11-hospital system located across Minnesota and Western Wisconsin. The cohorts were patients who were experiencing alcohol withdrawal based on assessment tool (CIWA-Ar) and treated for alcohol withdrawal symptoms using a variety of protocols in 2013–2015 (pre-MINDS group) versus patients who were assessed by the MINDS protocol in 2015–2017 and treated with benzodiazepines or high dose front-loading diazepam (MINDS group). The MINDS protocol was introduced system-wide in 2015 which was the overlapping year with the pre-MINDS protocols. All pre-MINDS protocols (16 active protocols in total, 3 were most commonly used, all with the CIWA-Ar assessment tool, and lower dose benzodiazepine dosing with lorazepam as the most common medication used) were terminated by the end of 2015.

Existing data were obtained from adult patients who consented to use of their electronic health records (EHR) for research. Eligible patients were ≥18 years of age, were eligible for the MINDS protocol, or previously had received CIWA protocols due to a diagnosis of acute alcohol withdrawal, had an ICD diagnosis for alcohol dependence or withdrawal, received an order set for alcohol withdrawal symptom assessment (CIWA or MINDS) and had any benzodiazepine administered. Patients who had a known allergy to benzodiazepines, were pregnant on admission, or had active withdrawal to benzodiazepines or stimulants were excluded.

Patient characteristics and outcomes

Patient covariates assessed were age, gender, race, marital status, insurance coverage, heart rate, body mass index (BMI), Severity of Illness, and Risk of Mortality with Minor, Moderate, Major, and Extreme categories. Insurance coverage was categorized into public insurance (Medicaid, Medicare, and Prepaid Medical Assistance Program, PMAP) and private insurance which included all other categories. The primary outcomes were hospital length of stay (LOS), in-hospital mortality, and all-cause mortality within 30 days post-hospital discharge. The secondary outcomes were emergency department (ED) or all-cause readmissions within 30 days, use of restraints, calendar days of administration and total dose administered of benzodiazepines, intensive care unit (ICU) admission or transfer, number of ICU stays, and discharge status.

Statistical analysis

Medians and interquartile ranges, proportions, and counts were calculated for the patient characteristics and outcome variables for the pre-MINDS and MINDS groups. Patients with missing data were excluded from

statistical analyzes. Chi-squared, Fisher's exact, Mann-Whitney, and two-sample independent t-tests were conducted as appropriate to compare the variables across the MINDS and pre-MINDS groups. Regression analyzes were performed to evaluate the relationships between implementation of the MINDS protocol and the outcome variables while adjusting for patient characteristics. All patient characteristics that were significant at the 0.1 level were included in the initial regression models. The covariates in the final modes were selected using a stepwise Akaike information criterion (AIC) elimination method for building the models. The four categories of Severity of Illness and Risk of Mortality were collapsed into two, levels 1 and 2 in one category and levels 3 and 4 in a second category. Negative binomial regression models were used to evaluate total benzodiazepine dose and days on benzodiazepines. A multiple linear regression model was used to assess hospital length of stay with a natural log transformation. After adjusting for the covariates, logistic regression models were used to evaluate the use of restraints, 30-day all-cause readmission, 30-day mortality, and ICU stay. Significance level was determined at $p < 0.05$.

RESULTS

From 2013 to 2015, 8218 patients were admitted to the hospital and treated with pre-MINDS protocols. From 2015 to 2017, 5409 hospitalized patients were treated with the MINDS protocol (Table 1). Compared to pre-MINDS patients, those who were treated with the MINDS protocol were older (median age of 49 versus 48 years), a lower proportion were female (32.4% versus 35.9%), and a higher proportion had public insurance coverage (63.9% versus 61.2%). The median heart rate was higher for MINDS patients (82 beats per minute, bpm) compared to pre-MINDS patients (80 bpm). The median BMI was also higher for MINDS patients than for pre-MINDS patients (26.5 versus 26.3). Higher proportions of MINDS patients than pre-MINDS patients were in the major (27.9% versus 22.4%) and extreme (9.3% versus 6.4%) categories for both Severity of Illness and Risk of Mortality (Table 2). Race and marital status did not significantly differ between the MINDS and pre-MINDS patients.

In the unadjusted outcomes, MINDS patients had a shorter median hospital length of stay (3.37 versus pre-MINDS: 3.99), and had significantly fewer total number of days on benzodiazepines. A higher proportion of MINDS patients were also discharged to home (74.2% versus 72.7%). A higher proportion of MINDS (17.1%) compared to pre-MINDS (15.2%) patients were admitted or transferred into the ICU and died within 30 days after hospital discharge (2.1% versus 1.4%). No significant differences were found between MINDS and pre-MINDS patients for ICU length of stay, 30-day readmission (both to the emergency department and to the hospital), total benzodiazepine dose administered, use of restraints, and in-hospital mortality (Table 2).

Table 1. Numbers (n) of hospitalized patients from 2013 to 2017 who received pre-MINDS versus MINDS treatment for alcohol withdrawal.

	Year					
Treatment	**2013**	**2014**	**2015**	**2016**	**2017**	**Total, *n***
Pre-MINDS	2993	2870	2355	0	0	8218
MINDS	0	0	594	2384	2431	5409
Total, n	2993	2870	2949	2384	2431	13627

After adjustment for the covariates using regression models, MINDS patients had a shorter hospital length of stay (exponentiated coefficient 0.83) and fewer days on benzodiazepines (incident rate ratio 0.79). MINDS patients were less likely to have restraints used (adjusted odds ratio, AOR = 0.8) and were more likely to be readmitted to the hospital within 30 days (AOR = 1.13), (Table 3). Total dose of benzodiazepines (diazepam equivalent) administered, rates for in-hospital all-cause mortality and for mortality within 30 days after hospital discharge, and ICU admission rates were not significantly different between MINDS and pre-MINDS patients.

DISCUSSION

In this single health system (11 hospitals) pre-post intervention cohort study, a MINDS assessment with a high-dose front loading diazepam based alcohol withdrawal treatment protocol (Figure 1) was associated with a reduced length of stay and fewer days on benzodiazepines. Other important positive outcomes included a reduction in use of physical restraints due to uncontrolled alcohol withdrawal-related behavior symptoms. Notably, total dose of diazepam equivalent in both groups were similar and use of the MINDS based protocol with front loading strategy did not increase sedation related complications including ICU care and mortality.

High dose diazepam with a front loading approach is the unique aspect and strength of our alcohol withdrawal treatment protocol. MINDS assessment was another key change compared to previous CIWA-Ar. MINDS assessment has less subjective components compared to CIWA-Ar (e.g. nausea, headache, anxiety) and relies more on objective measures. MINDS assessment score ranges from 0−46. With this protocol we use initial loading dose of 20 mg for MINDS score of 7−13, 40 mg for MINDS score of 14−20 and 80 mg for MINDS score more than 20. Similar dosing can be used at 1 h if MINDS score remains high. After that subsequent doses range from 10−40 mg and are allowed every 4 h as needed.

Studies with fewer patients have compared long acting and short acting benzodiazepines for treatment of alcohol withdrawal and have failed to show the benefit of one over the other.[15] However, diazepam is generally considered to provide smoother withdrawal and is slightly less expensive than lorazepam.[16, 18]

The finding that total dose of diazepam equivalent was similar in both groups while days receiving benzodiazepines were shorter in MINDS groups highlights the

Table 2. Characteristics of patients in Pre-MINDS versus MINDS group

Variables	Pre-MINDS Years 2013–2015	MINDS Years 2015–2017	*p*-values
Demographics			
Number of patient admissions (n)	8218	5409	
Age in years, median (Q1 – Q3)	48 (37–57)	49 (38–58)	<0.001
Female, % (n)	35.9% (2947)	32.4% (1750)	<0.001
Race, % (n):			0.12
White	90.2% (7354)	90.9% (4864)	
African American	5.6% (460)	5.5% (294)	
American Indian/ Alaska Native	3.7% (304)	3.0% (161)	
Asian, Native Hawaiian, Pacific Islander	0.5% (39)	0.6% (31)	
Married, % (n)	23.9% (1954)	24.9% (1341)	0.17
Insurance Coverage, % (n):			0.002
Private	38.8% (3188)	36.1% (1954)	
Public	61.2% (5030)	63.9% (3455)	
Heart rate, median (Q1 – Q3)	80 (71–91)	82 (72–92)	<0.001
BMI, median (Q1 – Q3)	26.3 (23.0–30.2)	26.5 (23.1–30.7)	0.04
Severity of Illness, % (n)			<0.001
1: Minor	20.4% (1064)	14.8% (792)	
2: Moderate	50.9% (2661)	48.0% (2575)	
3: Major	22.4% (1168)	27.9% (1500)	
4: Extreme	6.4% (332)	9.3% (502)	
Risk of Mortality, % (n)			<0.001
1: Minor	58.7% (3065)	46.2% (2482)	
2: Moderate	25.6% (1337)	32.9% (1765)	
3: Major	10.6% (552)	12.5% (672)	
4: Extreme	5.2% (271)	8.4% (450)	
Unadjusted Outcomes			
ICU admission or transfer, % (n)	15.2% (1246)	17.1% (925)	0.002
ICU LOS, days, median (Q1 – Q3)	1.79 (0.96–3.57)	1.86 (1.01–3.69)	0.43
30-day Readmission, (%) n	18.6% (1530)	19.8% (1070)	0.09
Hospital length of stay, days, median (Q1 – Q)	3.99 (2.50–6.66)	3.37 (2.05–5.79)	<0.001
All-cause 30-day mortality, % (n)	1.36% (112)	2.07% (112)	0.002
In-hospital mortality, % (n)	0.9% (70)	1.1% (62)	0.09
Use of restraints, % (n)	9.6% (789)	10.0% (543)	0.4
Total dose diazepam equivalent, median (Q1 – Q3)	64 (25–130)	64 (28–130)	0.17
Days receiving benzodiazepines, median (Q1 – Q3)	2 (1–4)	2 (1–3)	<0.001
Discharge to home, % (n)	72.7% (3800)	74.2% (4016)	0.017

BMI: Body mass index, ED: emergency department, ICU: intensive care unit.

Table 3. Association between application of the MINDS protocol and outcomes using regression analyzes.

Variable	Values	95% CI	*p*-values	n
Adjusted Odds Ratio				
Use of Restraints	0.80	[0.70–0.92]	0.002	10459
30-day all-cause readmission	1.13	[1.03–1.26]	0.014	10459
30-day Mortality	1.10	[0.81–1.50]	0.534	10459
ICU stay	1.03	[0.91–1.15]	0.659	10459
Exponentiated Coefficient				
Hospital LOS, in hours, natural log transformed	0.83	[0.81–0.85]	<0.001	10459
Incidence Rate Ratios				
Total benzodiazepine dose	0.97	[0.93–1.01]	0.135	10241
Days on benzodiazepine	0.79	[0.76–0.81]	<0.001	10459

CI: confidence interval, ICU: intensive care unit, LOS: length of stay.

hypothesis that goal of early aggressive treatment of alcohol withdrawal symptoms with longer acting benzodiazepine has potential to improve patient outcomes. While caring for hospitalized patients who experience alcohol withdrawal days on benzodiazepine is an important factor in symptom triggered therapy as it frequently helps treating clinician about discharge planning.

In our study, use of physical restraints decreased with use of the novel MINDS protocol. Physical restraints are very challenging part of any patient's care. They are not only hard on patients but also associated with distress among family members and care providing staff. Physical restraints have been linked to minor injuries such as sores and abrasions and can have a more significant inverse health impact including intensification of agitation.[19] Recent study indicated physical restraint use among

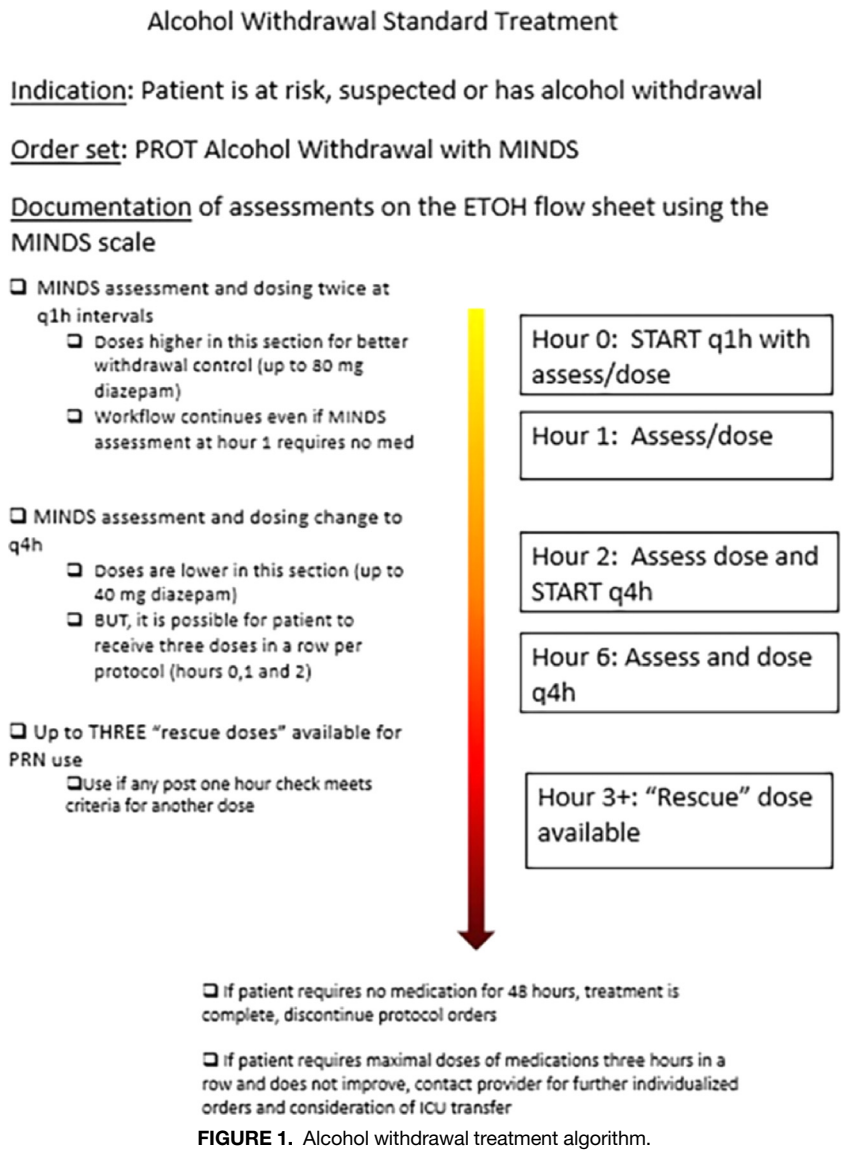

FIGURE 1. Alcohol withdrawal treatment algorithm.

psychiatric inpatients was associated with increased risk of deep vein thrombosis and aspiration pneumonia.[20] Appropriate pharmacological management and staff education are recommended strategies to reduce restraint use.[21] Minimizing the use of restraints can improve the quality of the patient experience, reduce physical and psychological harm, and improve patient safety.[22]

Based on discussion with clinicians and nursing staff it was felt that the new protocol was easier to administer and more effective at controlling withdrawal symptoms though we did not do any formal surveys.

In our study for patients in MINDS group, 30-day readmission risk was slightly increased. Though we do not have clear explanation for this finding, it is possible early discharge with symptom improvement could have resulted in rebound of symptoms in some patients. We also had higher proportion of patients with public insurance coverage compared to pre-MINDS patients. Public insurance coverage can be considered as a measure of socioeconomic status. Previous studies have shown patients with low income or with no insurance or Medicaid has increased readmission rates.[23] Other substance abuse are also risk factors for increased readmissions.[24] A strong association has been observed between discharge against medical advice and hospital readmissions.[25] Other substance abuse disorders including opioid use disorder is common among patient suffering from alcohol use disorder. Our study period was across several years during which the prevalence of opioid use disorder increased. We did not evaluate the effects of multiple substance use disorders or discharge against medical advice on risk of readmission for the patients in this study and these factors may have influenced our outcomes.

In summary, we found that MINDS assessment with high dose front loading diazepam improved hospital length of stay and physical restraint use without major adverse outcomes in hospitalized patients experiencing alcohol withdrawal symptoms.

LIMITATIONS

Limitations of this study include the single hospital system design which may limit generalization of these findings and the retrospective study design which limits the determination of a cause and effect relationship for the assessed variables. We are also comparing few protocols with CIWA-Ar assessment and variety of benzodiazepines against single protocol with MINDS assessment and diazepam which makes the attribution to any single factor difficult. Another factor to consider is despite the goal of high dose front loading long acting benzodiazepine use, we also ended up standardizing care and reducing variation which could have impacted the outcome. Though we believe as both groups received similar amount of benzodiazepines (diazepam equivalents), it is more likely that a front loading strategy led to better outcomes rather than standardization.

Intravenous dose of diazepam allows more predictable pharmacokinetics and achievement of peak effect rapidly which is beneficial for rapid control of severe alcohol withdrawal symptoms. Even for high MINDS score of >20 our protocol advises nurses to use oral diazepam if patient are able to safely take oral medications. This reduces the ability to more closely titrate and achieve peak effects rapidly. Future studies should assess this specific area and the effects of intravenous diazepam in severe alcohol withdrawal symptoms.

Despite the above limitations, our study suggests that a higher dose front loading strategy of long acting diazepam can be safely used with beneficial outcomes in alcohol withdrawal patients requiring hospitalization.

DECLARATION OF COMPETING INTEREST

None.

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