OBSERVATIONAL STUDY

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Phenobarbital-Based Protocol for Alcohol Withdrawal Syndrome in a Medical ICU: Pre-Post Implementation Study

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OBJECTIVES: We assessed the efficacy and safety of PB compared with benzodiazepine (BZD)-based protocols in treating AWS in MICU.

DESIGN: Single-center, pre-post protocol implementation study.

SETTING: The setting is a forty-bed MICU in a tertiary-level academic medical center.

PATIENTS: We included all patients admitted to the MICU with a primary diagnosis of AWS.

INTERVENTIONS: Intravenous PB 260 mg followed by 130-mg doses every 15–30 minutes as needed up to 15 mg/kg of ideal body weight versus escalating doses of BZD, to achieve a Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score less than 10.

MEASUREMENTS AND MAIN RESULTS: ICU and hospital length of stay (LOS), in addition to safety measures were the main outcomes of the study. A total of 102 patients were included, 51 in the PB arm and 51 in the BZD arm. There were no differences in baseline clinical characteristics. Half the patients in each group were admitted with delirium tremens. The use of PB-based protocol was associated with 35% reduction in median ICU LOS (1.5 d [interquartile range, 1.2–2.4 d] vs 2.3 d [1.4–4.8 d]; $p = 0.009$) and 50% reduction in hospital LOS (3 d [2.7–4 d] vs 6 d [4–10 d]; $p < 0.001$). After adjustment for comorbidities and clinical factors, PB protocol decreased ICU LOS days by 40% (95% CI; 25.8–53.5%). PB group required fewer adjunctive medications to control symptoms (0.7 [0.5–1] vs 2.5 [2–3]; $p < 0.001$), less need for intubation (1/51 [2%] vs 10/10 [19.6%]; $p = 0.023$) and less need for physical restraint (19/51 [37.3%] vs 29/51 [56.9%]; $p = 0.047$), compared with the BZD group.

CONCLUSIONS: A protocol utilizing rapidly escalating doses of PB over a short period is an effective and safe alternative to BZD in treating AWS in MICU.

KEY WORDS: alcohol withdrawal delirium; alcohol withdrawal syndrome; delirium tremens; intensive care units; phenobarbital

Alcohol withdrawal syndrome (AWS) encompasses a spectrum of symptoms that develop after either sudden cessation or abrupt reduction of alcohol intake in long-term alcohol users (1). Symptoms can range from mild, such as anxiety and tremors, to severe or fatal, including delirium tremens (DTs) and seizures, which occur in approximately 20% of patients admitted to the hospital with AWS (2, 3). AWS is associated with up to 10% of annual Medical ICU (MICU) admissions (4), and the burden associated with this diagnosis exceeds 250 billion dollars annually (5).

Historically, benzodiazepines (BZDs) are used as a first-line therapy in AWS due to their cross-tolerance with alcohol and their ability to acutely

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KEY POINTS

Question: Is a phenobarbital (PB)-based protocol an effective and safe alternative to benzodiazepines (BZD) in treating alcohol withdrawal syndrome (AWS) in the medical ICU (MICU)?

Findings: In this pre-post protocol implementation retrospective study, the PB-based protocol significantly decreased the MICU length of stay by 40% compared with the BZD protocol after controlling for comorbidities and clinical factors.

Meaning: PB-based protocol is an effective and safe alternative to BZD for treating AWS in MICU.

achieve anxiolysis by modulating the gamma-amino butyric acid (GABA-A) receptors (6). Resistant AWS (RAWS), where patients exhibit tolerance to BZDs and need alternative or adjunct therapies, is a common problem because of low levels of endogenous GABA and acquired conformational changes in the GABA receptor in chronic alcoholics (7). The definition and prevalence of RAWS are not consistent in the literature but range from 20% to 80% (7–9). For that reason, there has been substantial attention in identifying alternative medications that could substitute for or supplement BZD as a first line in AWS management, especially in critically ill patients (7). Phenobarbital (PB) is one such medication that has increased in popularity in the treatment of AWS (10) due to the dual mechanism of action: independent GABA receptor activation and antagonism excitatory glutamate receptors (11). In addition, PB has long duration of action (approximately 3–4 days), and predictable pharmacokinetics and pharmacodynamics, which makes it easily titratable and gives it a good safety profile in modest doses (12).

PB has been studied mainly in the emergency department (ED) and has been shown to decrease the need for ICU admission and is associated with a shorter ED length of stay (LOS) (13–16). Initial studies in the ICU have had inconsistent results, which are largely driven by a lack of a standardized protocol for PB administration, small heterogeneous populations, and extensive concomitant BZD administration (17–20). As a result, there are no strong evidence-based recommendations for the use of a PB-based protocol to treat AWS. We describe the results of the pre-post study, examining the efficacy and safety of a PB-based protocol in treating AWS in our MICU compared with a conventional BZD-driven protocol.

MATERIALS AND METHODS

Study Design and Setting

This is a pre-post protocol implementation, retrospective study at a 40-bed medical ICU in a nonprofit, multispecialty tertiary academic medical center. The study included all MICU patients admitted from January 2019 to February 2022 with a primary diagnosis of AWS. AWS symptoms necessitating ICU admission criteria can be defined as either uncomplicated (severe agitation, anxiety, tremors, tachycardia, and possible high blood pressure, requiring high-level nursing care) or severe: (DTs and/or alcohol withdrawal seizures). DTs is defined as fluctuating disturbance of attention and cognition, sometimes with hallucinations, in the presence of alcohol withdrawal, and is accompanied by agitation and signs of extreme autonomic hyperactivity. An alcohol withdrawal seizure is defined as a seizure that occurs within 6–48 hours after a person either stops drinking or significantly reduces the amount of alcohol they consume. Patients with mild symptoms or those at risk for severe or complicated AWS are managed in the medical floor of our hospital.

The study was reviewed and approved by the institutional review board (IRB) of the Cleveland Clinic Foundation (IRB 20-1129, approved on October 27, 2020, under the title "Phenobarbital in Alcohol Withdrawal Syndrome Management in Medical Intensive Care Unit"). Informed consent has been waived by the IRB. All procedures were in accordance with the ethical standards of the institutional IRB and with the Helsinki Declaration of 1975.

Implementation of the Phenobarbital Protocol

The standard of care in our institution for AWS was using a symptom-triggered BZD protocol depending on the Clinical Institute Withdrawal Assessment Alcohol Scale-Revised (CIWA-Ar) (**Supplemental Table 1**, http://links.lww.com/CCX/B173). The BZD protocol is implemented as an order set for both the medical floor and MICU, aiming to guide the nurses

to administer the BZD. In case the patient's symptoms remained not controlled, the decision of further BZD doses or using different medication was left to the physician's discretion without limitation for the total BZD dose. On September 2020, a new PB-based protocol was implemented. The protocol used an initial intravenous (IV) dose of PB 260 mg followed by repeated doses of 130 mg of PB every 15–30 minutes as needed up to 15 mg/kg of ideal body weight aimed at achieving a CIWA-Ar score of less than 10 (**Supplemental Fig. 1**, http://links.lww.com/CCX/B173). After the implementation, the clinical teams were encouraged to use the protocol as a first-line intervention. Extensive physician and nursing education were undertaken to make sure that the clinical teams were comfortable with this new protocol. The BZD protocol was available to use based on intensivist discretion or if the patient had contraindications to PB use. Once the patient was started on the PB-based protocol, further doses of BZD were prohibited for the duration the patient was on the PB-based protocol.

Data Identification and Extraction

Eligible patients were identified by searching the electronic medical record for MICU admissions with AWS in the problem list, using the appropriate *International Classification of Diseases*, 10th Edition codes during the study period. Furthermore, all patients who received PB or BZDs associated with AWS order sets in Medication Administration Record were examined for eligibility. All included records were then manually reviewed to determine that all included patients met the inclusion and exclusion criteria for the study. For our analysis, patients who were not directly admitted from the hospital's ED to the MICU, patients intubated prior to MICU admission, pregnant patients, patients who left against medical advice, those whose AWS was not the main reason for MICU admission, patients with a different key diagnosis that would have otherwise required ICU admission, and patients with a contraindication for PB use were excluded. Data were stored directly in Research Electronic Data Capture (REDCap). To ensure consistency and accuracy in the review and collection of data, the research team received standardized training in the form of biweekly meetings. The training sessions were conducted by the first author and included detailed explanation of the REDCap tool and written instructions. The first author also reviewed all entered data weekly and provided feedback to the whole data collection team (coauthors D.A., T.S., and S.A.) on any inaccuracies that were corrected.

We collected patient demographics, baseline clinical characteristics, comorbidities, last known alcohol consumption, prior AWS hospital admission, and initial laboratories at MICU admission including the level of sodium, alanine transaminase (ALT), aspartate aminotransferase (AST), AST/ALT, lactate, anion gap, and mean corpuscular volume. We also collected initial AWS symptoms at MICU admission and the CIWA-Ar score at MICU admission, during the stay and at discharge from MICU. The primary outcome was ICU LOS in days. Secondary outcomes included hospital LOS days, intubation related to AWS, the number of adjunct medications to control AWS symptoms, ICU readmission during the same visit, the need for a sitter, physical restraints, and protocol-related side effects of hypotension and agranulocytosis.

Sample Size and Data Analysis

Based on historical data from our institution, the average ICU LOS for AWS was 3 days, with an SD of 2 days. To detect a 30% reduction in the primary outcome with a power of 80%, at a 5% one-sided type I error, a minimum of 50 patients per group was required. Normally distributed continuous variables were presented as mean and 95% CI, and an independent *t* test was used to examine the differences between the two groups. The engagement score was used to assess the normality distribution of the data, as assessed by the Shapiro-Wilk test. Nonnormal distributed data were presented as the median and interquartile range (IQR), and the Mann-Whitney *U* test was used to examine the groups' differences. Categorical variables were presented as counts and percentages, and the chi-square test or Fisher exact test was used to detect the significant differences between both groups. To determine the relationship between the intervention and ICU LOS with controlling available clinical covariates at the time of MICU admission, we conducted a multivariable linear regression analysis. Regression assumptions, such as normality, linearity, homoscedasticity, and absence of multicollinearity, were examined, and only the ICU LOS violated the normality assumption,

so a log transformation of the dependent variable, ICU LOS, was performed to achieve normality of distribution. The regression results are presented as a coefficient and 95% CI. Since the model is a log-level regression, to simplify the interpretation of the coefficient, for each one-unit increase in the independent variable (ID), we would expect the ICU LOS to change by 100 × ID coefficient %. All analyses were one-tailed and performed at a significance level of 0.05. International Business Machines Corporation Statistical Package for the Social Sciences Statistics for Windows (Version 26.0, IBM, Armonk, NY) was used for all analyses except the Kaplan-Meier curve to visualize the probability of ICU and hospital discharge over time, which were performed using R programming language Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

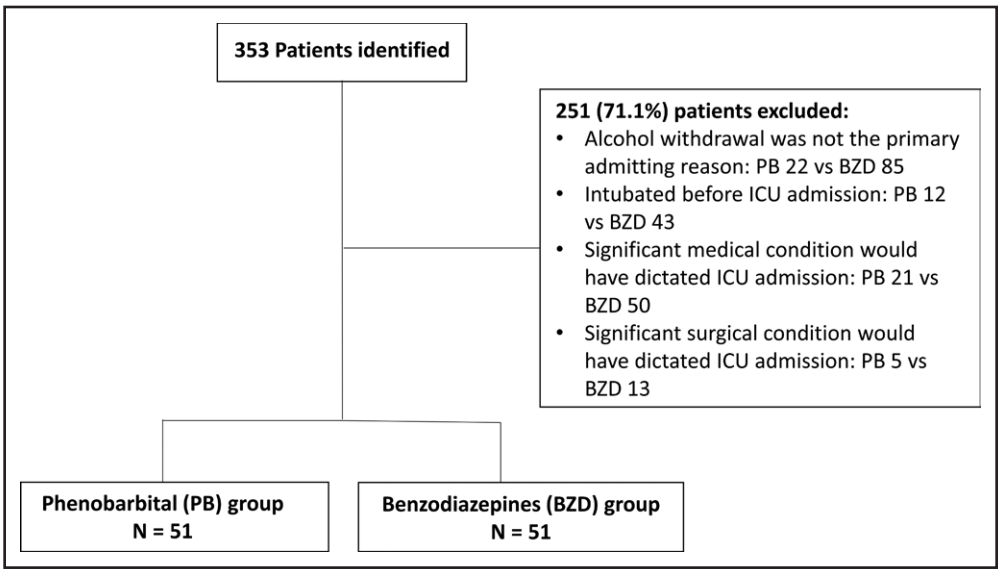

Figure 1. Flowchart for patient screening and exclusion. BZD = benzodiazepine, PB = phenobarbital.

RESULTS

Three hundred fifty-three medical records were screened to assess eligibility for the study. We excluded 251 patients, and the remaining 102 were included in this analysis (**Fig. 1**). In both groups, the majority of patients were middle-aged (mean 56 yr [95% CI, 52.7–59.3 yr] vs 54.5 yr [95% CI, 50.9–58.1 yr]; $p = 0.528$) and male (41 [80.4%] vs 37 [72.5%]; $p = 0.350$), PB vs BZD group, respectively. Approximately half of the patients in each group were admitted with DTs to the ICU, 40% with uncomplicated severe AWS, and 10% with seizures (**Table 1**). No statistically significant was found between both groups as regards other demographics, basic clinical characteristics, comorbidities, last alcohol intake, prior AWS admission, initial lab results, and initial CIWA-Ar score at ICU admission (Table 1).

Implementation of the PB-based protocol led to a decrease in the median ICU LOS days compared with the BZD group (1.5 d [IQR, 1.2–2.4 d] vs 2.3 [IQR, 1.4–4.8 d]; $p = 0.009$). For secondary outcomes, a decrease in median hospital LOS days was achieved in the PB group (3 d [IQR, 2.7–4 d] vs 6 d [IQR, 4–10 d]; $p < 0.001$). The use of a PB-based protocol led to an improved probability of discharge from the ICU and hospital over the time since admission (**Fig. 2**). The use of a PB-based protocol was also associated with better control of AWS symptoms and median maximum CIWA-Ar score during MICU stay (16 [IQR, 12–22] vs 21 [IQR, 15–27]; $p = 0.009$) and the median CIWA-Ar score at the time of MICU discharge (3 [IQR, 2–5] vs 5 [IQR, 3–8]; $p = 0.010$). In addition, PB led to a significant reduction in the average total number of adjunct medications used to control AWS by 72% (0.7 [95% CI, 0.5–1] vs 2.5 [95% CI, 2–3]; $p < 0.001$). **Table 2** summarizes the study outcomes, and **Figure 3** shows the differences between both groups as regards different adjunct medication, the need for a sitter, physical restrain, and mechanical ventilation to protect the airway.

A multivariable linear regression analysis was used to examine the effect of PB vs BZD protocol on the ICU LOS days after controlling for age, gender, body mass index, comorbidities, previous history of severe AWS admission, last exposure to alcohol, initial CIWA-Ar score in MICU, and presence of severe AWS at MICU admission (**Table 3**). After adjustment, PB vs BZD protocol led to a decrease in ICU LOS days by 40% (95% CI, 25.8–53.5). Factors associated with increased ICU LOS were male sex 23.2% (95% CI, 5.2–41.2) and severe AWS at MICU admission 22.8% (95% CI, 7.4–38.2). There was independence of residuals, as assessed by a

TABLE 1.

Demographics and Clinical Characteristics of Patients Who Received Phenobarbital-Based Protocol Versus Benzodiazepine-Based Protocol for Treating Alcohol Withdrawal Syndrome in Medical ICU

Clinical Characteristics	Phenobarbital ($n = 51$)	Benzodiazepines ($n = 51$)	p[d]
Age[a] (yr)	56 (52.7–59.3)	54.5 (50.9–58.1)	0.528
Male[b]	41 (80.4)	37 (72.5)	0.350
White[b]	45 (88.2)	41 (80.4)	0.128
Non-Hispanic[b]	50 (98)	50 (98)	1.000
Body mass index[a] (kg/m^2)	25 (23.6–26.5)	27.2 (25.6–28.9)	0.052
Comorbidities			
Diabetes mellitus[b]	8 (15.7)	6 (11.8)	0.565
Hypertension[b]	27 (52.9%)	24 (47.1)	0.552
Chronic obstructive pulmonary disease[b]	9 (17.6)	6 (11.8)	0.402
Liver disease[b]	10 (19.6)	9 (17.6)	0.799
Polysubstance abuse[b]	4 (7.8)	7 (13.7)	0.338
Chronic kidney disease[b]	0 (0)	3 (5.9)	0.243
Seizure disorder[b]	2 (3.9)	7 (13.7)	0.160
Psychiatric disorder[b]	13 (25.5)	19 (37.7)	0.200
Last alcohol intake, days[a]	1.6 (1.3–1.9)	1.6 (1.2–2)	0.825
Prior AWS admission			
Uncomplicated[b]	19 (37.3)	13 (25.5)	0.200
Delirium[b]	19 (37.3)	18 (35.3)	0.837
Seizure[b]	6 (11.8)	6 (11.8)	1.000
Initial laboratory			
Sodium[a] (mmol/L)	135.1 (133.3–136.8)	136.3 (133.8–138.9)	0.404
Aspartate transaminase/alanine transaminase[a]	2.2 (1.9–2.6)	2.3 (1.9–2.7)	0.730
Anion gap[a] (mmol/L)	18.2 (15.9–20.6)	21.2 (19.1–23.4)	0.064
Lactate[a] (mmol/L)	3.5 (2.8–4.3)	3.6 (2.8–4.3)	0.985
Mean corpuscular volume,[a] fL	94.8 (92.7–96.9)	96.3 (93.9–98.7)	0.346
Initial Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score in MICU[c]	11 (7–15)	9 (6–15)	0.571
AWS symptom at admission			
Uncomplicated[b]	21 (41.2)	20 (39.2)	0.840
Seizure[b]	6 (11.8)	7 (13.7)	0.767
Delirium[b]	24 (47.1)	24 (47.1)	1.000
Cumulative dosage in MICU, mg			
Lorazepam equivalent[c]	0 (0–0)	21 (15–28)	**< 0.001**
Phenobarbital[c]	520 (390–520)	0 (0–0)	**< 0.001**

AWS = alcohol withdrawal syndrome, MICU = medical ICU.

[a]Data are presented as mean (95% CI) and independent *t* test used for group comparison.

[b]Data are presented as count (percentage) and the χ^2 test or Fisher exact test used for group comparison.

[c]Data are presented as median (interquartile range) and Mann-Whitney *U* test used for group comparison.

[d]Boldface entries indicate statistically significant differences ($p < 0.05$) between both groups.

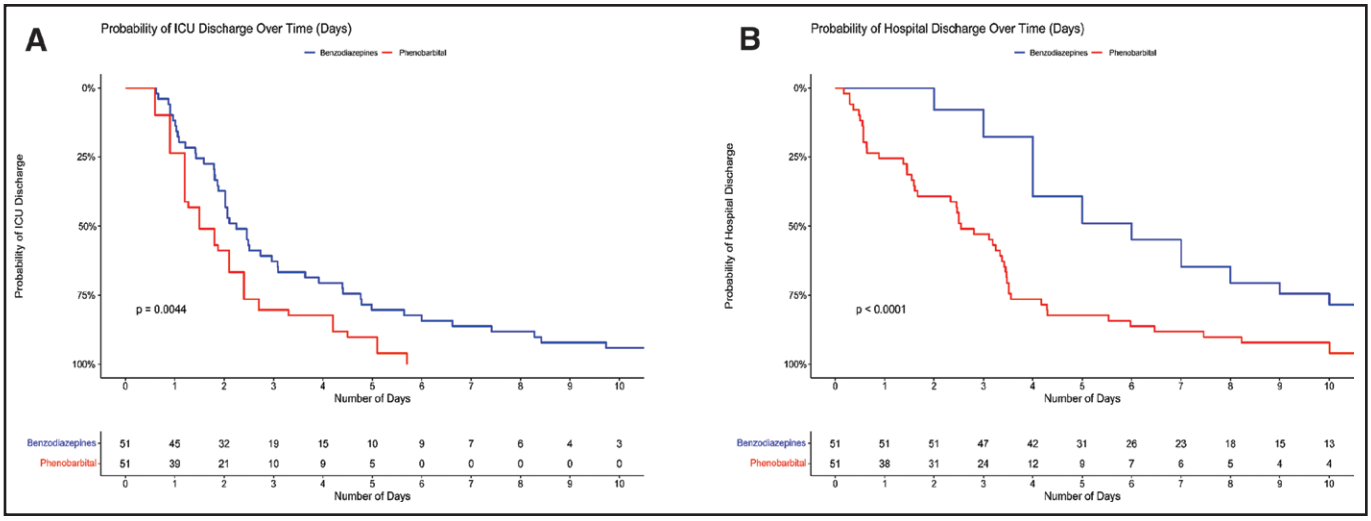

Figure 2. Kaplan-Meier curves for survival probability. Kaplan-Meier curves showing the probability of (**A**) ICU and (**B**) hospital discharge over time.

TABLE 2.
Primary and Secondary Outcomes

Outcomes	Phenobarbital (n = 51)	Benzodiazepines (n = 51)	*p*[d]
Primary outcome			
ICU LOS[a] (d)	1.5 (1.2–2.4)	2.3 (1.4–4.8)	**0.009**
Secondary outcome			
Hospital LOS[a] (d)	3 (2.7–4)	6 (4–10)	**< 0.001**
Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score control			
Maximum during MICU stay[a]	16 (12–22)	21 (15–27)	**0.009**
MICU discharge[a]	3 (2–5)	5 (3–8)	**0.010**
Safety			
Hypotension[b]	0 (0)	1 (2)	1.000
Agranulocytosis[b]	0 (0)	1 (2)	1.000
Sitter[b]	16 (31.4)	13 (25.5)	0.510
Restrain[b]	19 (37.3)	29 (56.9)	**0.047**
Need for mechanical ventilation[b]	1 (2)	10 (19.6)	**0.023**
MICU readmission[b]	3 (5.9)	3 (5.9)	1.000
Adjunct medications[c]	0.7 (0.5–1)	2.5 (2–3)	**< 0.001**
Dexmedetomidine[b]	13 (25.5)	24 (47.1)	**0.023**
Gabapentin[b]	6 (11.8)	39 (76.5)	**< 0.001**
Haloperidol[b]	11 (21.6)	31 (60.8)	**< 0.001**
Clonidine[b]	8 (15.7)	27 (52.9)	**< 0.001**
Valproic acid[b]	0 (0)	6 (11.8)	**0.027**

LOS = length of stay, MICU = medical ICU.
[a]Data are presented as median (interquartile range) and Mann-Whitney *U* test used for group comparison.
[b]Data are presented as count (percentage) and the χ^2 test or Fisher exact test used for group comparison.
[c]Data are presented as mean (95% CI) and independent *t* test used for group comparison.
[d]Boldface entries indicate statistically significant differences ($p < 0.05$) between both groups.

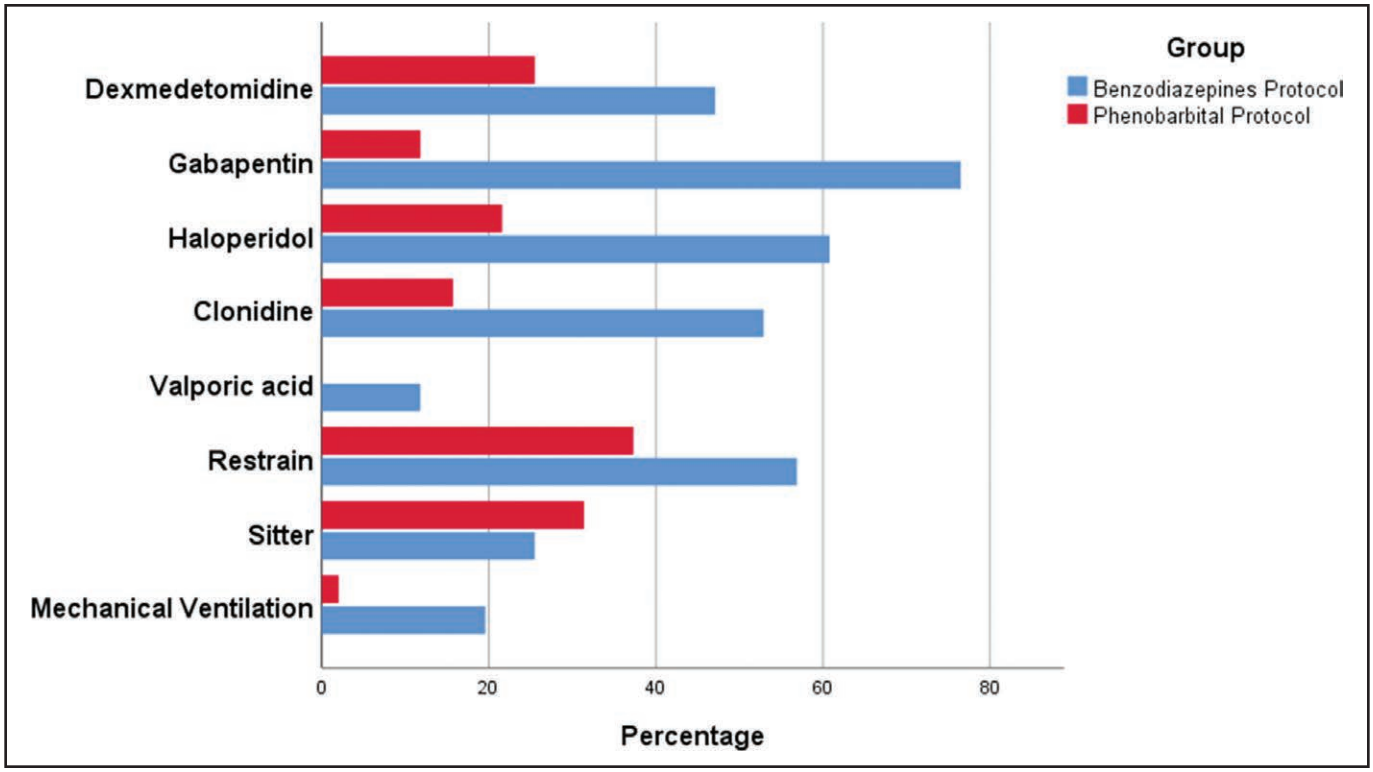

Figure 3. Clustered bar diagram for adjunct medications, physical restrain, sitter, and mechanical ventilation use for the patients on phenobarbital-based protocol versus benzodiazepine-based protocol.

TABLE 3.

Multivariable Linear Regression Analysis Assessing the Relationship Between Clinical Predictors and Log Outcome (ICU Length of Stay Days)

Predictors	Coefficients (95% CI)	*p*[a]
Phenobarbital- vs benzodiazepine-based protocol	−0.397 (−0.535 to −0.258)	< 0.001
Age (yr)	−0.001 (−0.007 to 0.005)	0.805
Male vs female	0.232 (0.052–0.412)	**0.012**
Body mass index (kg/m^2)	0.006 (−0.008 to 0.02)	0.389
Past medical history (positive vs negative)		
Diabetes mellitus	−0.13 (−0.346 to 0.087)	0.237
Hypertension	0.115 (−0.034 to 0.263)	0.128
Chronic obstructive lung disease	0.023 (−0.175 to 0.222)	0.814
Liver disease	0.086 (−0.095 to 0.267)	0.349
Polysubstance abuse	0.149 (−0.083 to 0.381)	0.206
Seizure disorder	0.135 (−0.116 to 0.386)	0.289
Psychiatric disorder	−0.034 (−0.2 to 0.132)	0.684
History of severe AWS vs uncomplicated/none	−0.077 (−0.229 to 0.075)	0.316
Last alcohol drink (d)	−0.001 (−0.049 to 0.046)	0.954
Initial Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score in MICU	−0.006 (−0.017 to 0.005)	0.306
Severe AWS presentation at MICU admission vs not severe	0.228 (0.074–0.382)	**0.004**

AWS = alcohol withdrawal syndrome, MICU = medical ICU.

[a]Boldface entries indicate statistically significant differences ($p < 0.05$) between both groups.

Durbin-Watson statistic of 1.57. R^2 for the overall model was 45.3% with an adjusted R^2 of 36%, which points to a substantial effect size, as described by Cohen (21).

DISCUSSION

In our pre-post protocol implementation study, the use of a PB-based protocol for the treatment of AWS was associated with a 40% decrease in the ICU LOS compared with the historic CIWA-Ar BZD-based protocol, after controlling for comorbidities and clinical factors. The use of a PB-based protocol was also associated with a 50% decrease in the median hospital LOS. The use of this protocol was associated with a 70% decrease in the need for adjunct medications for AWS.

The implementation of a protocol for the use of BZD and PB in the management of agitated and delirious patients in the ICU was shown to result in a significant reduction in ICU LOS by 46%, as reported by Duby et al (22). Although the effects of PB were not specifically evaluated in the study by Duby et al (22), the reduction in LOS observed in our study with the use of PB is consistent with the findings reported by Tidwell et al (20). Although there are dosage differences between our and Tidwell et al (20) protocol, the average used PB dose is similar, approximately 500 mg, which could explain the similarity in outcomes. Our protocol utilized only IV forms of PB as it is more convenient when the patient is actively in severe withdrawal, whereas Tidwell et al (20) combined IV and oral. Nguyen and Lam (18) published a study assessing PB as an adjunct to lorazepam vs lorazepam alone and could not detect significant differences in ICU and hospital LOS. This difference in outcomes is likely driven by the fact that in their protocol PB was used only as an adjunct, and the PB dose and frequency were left to the provider's discretion and not as part of a protocol. Furthermore, their study population included patients who developed AWS during the ICU admission course regardless of the reason for admission, which is a possible confounding factor with a risk of bias. Another study that contradicts our findings was conducted by Goodberlet et al (23), where the results were confounded by the severity of admission illness rather than AWS. In this study, only the Acute Physiology and Chronic Health Evaluation II score at admission was associated with prolonged LOS.

Our study shows an excellent safety profile for PB when used in escalating doses over a short time targeting symptomatic control. The significant decrease in the need for physical restraints and mechanical ventilation compared with BZD has been reported by Bosch et al (24) and Gold et al (17) in previous publications. Our study shows that PB is not associated with any increase in the risk of oversedation and the need for mechanical ventilation when used in AWS. Similar findings have been shown in other studies in the ICU (17, 24) and by randomized controlled trials in ED (25, 26). We only had one patient in the PB arm who required intubation to protect the airway because of vomiting with seizure. This finding is similar to what Hammond et al (10) reported in a systematic review, where most patients needed mechanical ventilation due to non-PB-related side effects.

The strengths of our study include the strict inclusion and exclusion criteria focusing on assessing PB-based protocol exclusively on AWS patients in MICU. Our study was powered appropriately, and as a result, we could control for a large number of confounders to assess the effect of PB more appropriately. The limitations of our study are driven by the fact that it is a single-center retrospective analysis. It is important to note that the implementation of the PB-based protocol in our hospital occurred during the COVID-19 pandemic, which may have had an impact on our results due to the potential for selection bias. Our hospital is part of a larger healthcare system, and cases were redirected to other facilities based on MICU availability, which could have affected the results. Finally, the use of CIWA-Ar in the MICU has been subject to debate in the literature, as it relies on patient cooperation (27). Our protocol was not specifically designed for the MICU and allows for further dosing discretion by physicians, which may affect the standardization of treatment and the overall efficacy of the protocol. We feel that by performing a multivariable regression analysis, we have addressed most of these limitations. Additionally, we acknowledge the relatively low total median BZD dose in our BZD group as a limitation, as it is possible that more aggressive BZD dosing might have improved outcomes in this group. Our study highlights that PB-based protocols achieve clinical effectiveness in treating AWS with few side effects. Continuous assessment of the currently implemented protocol is required to monitor if the benefit would be retained over time.

CONCLUSIONS

Rapidly escalating doses of PB over a short period are an effective and safe alternative to BZD in treating AWS in MICUs.

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