ORIGINAL ARTICLE

Characterization of Intravenous Ethanol Use for Alcohol-Dependent Patients in an Intensive Care Unit

NICK B. POLITO[1*], STEPHEN RAPPAPORT[2], KEVIN C. COOPER[2], KATHRYN A. CONNOR [2,3], MARIN VALENTINO[2], PARITOSH PRASAD[2],

[1]Highland Hospital·University of Rochester Medical Center,1000 South Ave, Rochester, NY 14620
[2]Strong Memorial Hospital, University of Rochester Medical Center,601 Elmwood Ave, Rochester, NY 14642
[3]Wegmans School of Pharmacy, St. John Fisher College, 3690 East Ave, Rochester, NY 14618

Abstract

Background: Little evidence supports intravenous ethanol (IVE) as an alternative alcohol withdrawal syndrome (AWS) prophylactic agent. This study characterized the use of IVE in alcohol dependent patients and described clinically relevant efficacy and safety outcomes.
Methods: Retrospective descriptive study of IVE use between January 1st, 2011 and September 15th, 2018 was carried out in this study. Patient characteristics, infusion parameters, and outcomes were recorded.
Results: In this study, 69 patients received IVE; 24 (34.8%) received IVE for AWS treatment. Percent infusion time outside goal Sedation-Agitation Scale (SAS) and Clinical Institute Withdrawal Assessment (CIWA) ranges were 4.8% (IQR 0 – 17.4) and 3.8% (IQR 0 – 9.8), respectively. Forty-two (60.9%) patients received a benzodiazepine with a median daily requirement of 0.72 mg (IQR 0 – 3.12) of lorazepam equivalent. Mechanical ventilation was associated with increased benzodiazepine dose ($p = 0.002$) and a higher percentage of time spent outside goal SAS ($p < 0.001$) range. Treatment patients required higher daily doses of IVE ($p = 0.05$) and spent more time outside of goal CIWA range ($p < 0.001$). Higher initial infusion rate was associated with intubation during infusion.
Conclusion: Patients spent a majority of infusion time within goal SAS and CIWA ranges and required low doses of benzodiazepines. Mechanical ventilation and indication were associated with significant differences in patient outcomes and are likely to be confounders for any future investigation utilizing benzodiazepine requirements or sedation or withdrawal scales as endpoints. Further study is required to elucidate the potential benefits and risks of IVE.

Key word: withdrawal, prophylaxis, critical care, alcohol, ethanol

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INTRODUCTION

Ethanol is the most commonly abused drug in the United States and across the world [1-3]. Abstinence can precipitate withdrawal in as little as 6-8 hours, which is estimated to occur in 25% of dependent patients upon cessation of alcohol intake and is seen in up to 40% of patients admitted to surgical intensive care units [4-7]. GABAergic agents are often used to treat alcohol withdrawal syndrome (AWS) with benzodiazepines considered the standard of care [1,6-10]. Intravenous ethanol (IVE) is an alternative agent that has been utilized for AWS prevention and treatment. IVE is thought to cause less sedation and respiratory depression than other GABAergic agents making it an attractive option in critically ill patients, however its administration to dependent patients poses an ethical dilemma [3-4,8-11]. Additionally, IVE is not without acute adverse effects as infusions may cause or exacerbate hypoglycemia and hyponatremia [11].

Previous studies investigating IVE use in alcohol withdrawal prophylaxis contain heterogeneous study populations, methods, outcomes, and IVE dosing, indication, and intent [11-16]. Results pertaining to the efficacy of IVE for AWS prophylaxis are conflicting and fail to definitively identify significant benefits over standard therapies [11-16]. Some authors report complete efficacy of IVE, while others report high prophylaxis failure rates, significant benzodiazepine use, and increased time spent outside of goal sedation range. However little contemporary data describes IVE infusion practices or outcomes [11-16]. Additionally, although IVE is not currently recommended nor commonly used for the management of AWS as its relative safety and efficacy is largely unknown, this may not be universally true outside the US and in relation to drug shortages [1]. Therefore, our aim was to characterize the use of IVE at our institution, describe important patient outcomes such as withdrawal avoidance, benzodiazepine use, time spent at goal sedation, and relevant safety endpoints. Lastly, we aimed to determine potential confounders for likely endpoints in future comparative studies.

*Correspondence to: Nick B. Polito, PhD, University of Rochester Medical Center, 1000 South Ave, Rochester, NY 14620
Email: nicholas_polito@urmc.rochester.edu, Tel: 585-276-9244 Fax: 585-341-9768

METHODS

Study Design and Setting

Retrospective chart review of all adult patients receiving IVE at the University of Rochester Medical Center Strong Memorial Hospital, an 850-bed tertiary care and Level I trauma center, between January 1st, 2011, and September 15th, 2018. The study protocol was approved by the University of Rochester Research Subjects Review Board (IRB). Patients were identified via an electronic inquiry of patient data from the electronic medical record (EPIC, Verona, WI, USA).

During the study period, our institution had a guideline in place, which specified that IVE was to be used only as an AWS prophylaxis agent with ordering restricted to attending physicians. The use of IVE necessitated a transfer to an ICU, although the infusion could have been initiated prior to arrival in the ICU. It was recommended that IVE be administered through a central line or that peripheral administration occur with a compatible IV fluid running at the same rate. The guideline recommended against IVE use in patients with baseline liver disease. Due to suspected non-adherence to the prophylaxis guideline, IVE was deemed to be utilized for treatment if it was initiated after a patient was transferred to the ICU to manage withdrawal symptoms or in any patient with a recorded CIWA score ≥ 10 prior to the start of the infusion. Patients confirmed to be receiving IVE for prophylaxis were determined to have failed prophylaxis if a CIWA score ≥ 10 was recorded at any point during IVE infusion. To determine if ICU admission or central line placement occurred for the sole purpose of accommodating IVE, two investigators independently assessed each patient case, with discordance amongst investigators adjudicated through a consensus meeting. Blood ethanol levels were not routinely monitored. All infusions were compounded as 10% (v/v %) ethyl alcohol intravenous solutions (0.079 g ethanol/mL) in D5W or 0.45% saline by the inpatient pharmacy. The guideline recommended a starting infusion rate between 0.5 to 1.0 mL/kg/hr. with the infusion titrated off as tolerated over 72 hours. Initial IVE dosing and titration were left up to the discretion of the attending provider, no standardized nursing protocol drove the titration of the infusion. Adjunctive AWS agents, including benzodiazepines, used for the management of AWS symptoms and sedation of intubated patients were administered as needed or based on our institution's CIWA protocol with selection and dosing of specific agents determined by individual providers. Our CIWA protocol recommended 10-20 mg of oral diazepam every hour or 2-4 mg of IV lorazepam every hour for CIWA scores between 10-15. For CIWA scores of 16 or more 2-4 mg of IV lorazepam every half hour was recommended with phenobarbital considered for CIWA scores exceeding 20. Due to cost and difficulties associated with compounding IVE, this guideline is no longer active and IVE is not available at our institution.

Inclusion and Exclusion Criteria

We included all patients that received IVE for AWS prophylaxis or treatment in the present study. However, it is noteworthy that there were no exclusion criteria in the sample selection.

Data Collection

Patient demographics, past medical history, length of intensive care unit (ICU) stay, and presence of mechanical ventilation while receiving IVE infusion were electronically recorded. Reason for hospitalization, IVE dosing, administration, and dosing of concomitant medications used for sedation and management of AWS, CIWA and SAS scores, laboratory values and need for intubation during IVE infusion were collected manually [17,18]. CIWA and SAS scores were evaluated for each hour of the IVE infusion with missing data being assessed using the last value carried forward method. CIWA scores were only collected for patients, who were not mechanically ventilated while receiving IVE. Goal CIWA and SAS ranges during IVE infusion were < 10 and 3 or 4, respectively. CIWA scores were typically assessed by nursing staff every 8 hours with more frequent assessments occurring every 2 hours for patients with a recent CIWA score greater than or equal to 10. SAS scores were obtained with vital signs either hourly or every other hour as ordered. The primary endpoints were time spent within goal Sedation-Agitation Scale (SAS) and Clinical Institute Withdrawal Assessment (CIWA) ranges and benzodiazepine use while receiving IVE. Secondary endpoints included identification of confounders of the primary endpoints for future comparative studies. Hypoglycemia and hyponatremia during IVE treatment were recorded as safety endpoints with need for on treatment intubation being identified as a *post-hoc* safety outcome.

Statistical Analysis

Descriptive statistics were used to analyze univariate data. All univariate descriptors were displayed as median and interquartile range or number and percentage. Spearman correlation, Fisher exact, and unpaired two sample Wilcoxon tests were used to identify relevant associations. Logistic regression models were used to examine the influence of potential confounders between significant associations. P-values less than 0.05 were considered to be statistically significant. All analyses were carried out using R 3.5.0 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R -project.org/).

RESULTS

A total of 69 patients received IVE during the study period (Table 1). The most common reason for hospital admission was non-emergent surgery. Thoracic (53.6%), trauma (13.0%), and vascular surgery (10.1%) were the most frequent services to initiate IVE therapy. IVE was administered to seven patients with hepatitis and four patients with cirrhosis at baseline.

Patient data related to the IVE infusion is listed in Table 2. Of the sample, 26 patients (37.7%) were admitted to the ICU for the sole purpose of accommodating IVE. IVE was administered via central venous access in 27 (39.1%) patients

with 6 (22.2%) having central venous access obtained solely to administer IVE. IVE was used for AWS prophylaxis in 45 (65.2%) patients. Four (8.9%) prophylaxis patients experienced prophylaxis failure. Patient body weight was the only demographic associated with initial IVE dose ($r_s = 0.24$, $p = 0.04$). A minority of patients needed an up-titration of IVE infusion rate. Median duration of IVE infusion was 78 hours.

Results from the primary outcomes and safety endpoints can be found in Table 3. Patients spent a majority of IVE infusion time within goal SAS and CIWA range. A majority (61.6%) of the time spent outside goal SAS range was spent above goal. Most patients (60.9%) received at least one dose of a benzodiazepine during IVE infusion. However, the overall benzodiazepine requirements were low. Hypoglycemia and hyponatremia were recorded in approximately 10% of patients with no relationship existing between duration of ethanol infusion and the occurrence of these adverse events.

Significant differences were observed between patients, who were mechanically ventilated during IVE infusion and

Table 1. Demographics and baseline characteristics of patients receiving IVE

	Study Population (n = 69)
Age (years), median (IQR)	59 (54-65)
Male, n (%)	60 (87.0)
Race (white), n (%)	61 (88.4)
Weight (kg), median (IQR)	80 (70 – 93)
Reported drinks per day, n (%)	6 (4-10)
Reason for hospitalization	
Non-emergent surgery, n (%)	39 (56.5)
Medical, n (%)	14 (20.3)
Trauma, n (%)	9 (13.0)
Emergent surgery, n (%)	7 (10.1)
Baseline ethanol level obtained, n (%)	14 (20.3)
Positive baseline ethanol level, n (%)	9 (13.0)
Covering Service at the start of IVE	
Thoracic, n (%)	37 (53.6)
Trauma, n (%)	9 (13.0)
Vascular surgery, n (%)	7 (10.1)
Other, n (%)	16 (23.2)
Past medical history	
Tobacco use, n (%)	54 (78.3)
Cancer, n (%)	36 (52.2)
History of withdrawal, n (%)	8 (11.6)
Hepatitis, n (%)	7 (10.1)
Cirrhosis, n (%)	4 (5.8)
Invasive mechanical ventilation prior to receiving IVE, n (%)	14 (20.3)

IVE = intravenous ethanol IQR = interquartile range
Data are reported as n (%) or median (interquartile range)

Table 2. Data pertaining to patient admission, IVE infusion and collection of SAS and CIWA scores

	Study Population (n = 69)
IVE initiated for treatment of AWS, n (%)	24 (34.8)
ICU admission only to accommodate IVE, n (%)	26 (37.7)
IVE administration via central line, n (%)	27 (39.1)
Central access placed only to accommodate IVE, n (%)	6 (22.2)
Initial rate (g ethanol/hr.), median (IQR)	4.7 (4.0 – 5.9)
Duration of infusion (hrs.), median (IQR)	78 (54 – 99)
Length of ICU stay (hrs.), median (IQR)	211 (101-503)
Daily volume of ethanol infused (mL), median (IQR)	1035 (712 - 2760)
Patients requiring up-titration of IVE, n (%)	27 (39.1)
Non-ventilated patients with CIWA score during infusion, n (%)	35 (50.7)
Percent of infusion time spent outside goal CIWA score, median (IQR)	3.8 (0 – 9.8)
Prophylaxis patients with at least one recorded CIWA ≥ 10, no./tot. (%)	4/21 (19.0)
Patients with SAS score during infusion, n (%)	67 (97.1)
Mechanical ventilation during IVE infusion, n (%)	29 (42.0)
Concomitant Medications	
Benzodiazepines, n (%)	42 (60.9)
Antipsychotics, n (%)	19 (27.5)
Dexmedetomidine, n (%)	15 (21.7)
Gabapentin, n (%)	9 (13.0)
Propofol, n (%)	9 (13.0)
Barbiturates, n (%)	3 (4.3)
Clonidine, n (%)	3 (4.3)
Ketamine, n (%)	3 (4.3)

IVE = intravenous ethanol AWS = alcohol withdrawal syndrome ICU = intensive care unit CIWA = Clinical Institute Withdrawal Assessment IQR = interquartile range SAS = Sedation and Agitation Score
Data are reported as n (%) or median (interquartile range)

Table 3. Primary efficacy and safety outcomes for patient receiving IVE

Primary Efficacy Outcomes	
Percent of infusion time spent outside goal SAS score, median (IQR)	4.8 (0 – 17.4)
Percent of infusion time spent with SAS > 4, median (IQR)	3.9 (0 – 11.2)
Percent of infusion time spent with SAS < 3, median (IQR)	0 (0 – 1.1)
Percent of infusion time spent outside goal CIWA score, median (IQR)	3.8 (0 – 9.8)
Lorazepam equivalent per day (mg/day), median (IQR)	0.72 (0 – 3.12)
Safety Outcomes, n (%)	
Hypoglycemia (< 70 mg/dL)	7 (10.1)
Hyponatremia (< 130 mEq/L)	8 (11.6)
On-treatment intubation (*post-hoc)*	15 (21.7)

those, who were not. An increase in benzodiazepine dose requirements and percent of infusion spent outside of goal SAS was observed in patients, who were mechanically ventilated (Table 4). Ventilated patients spent a majority (55.8%) of time outside of goal SAS score above the goal range. Initial IVE infusion rate was associated with on-treatment intubation (p = 0.006). A *post-hoc* multivariate logistic regression was performed to examine the relationship between on-treatment intubation and patient weight, presence of up titration of IVE infusion and initial IVE infusion rate. Initial rate (mL/hr.) remained the only significant independent predictor for on-treatment intubation (OR [95% CI]; 1.043 [1.009 – 1.084]). No patient receiving an initial IVE infusion rate between 25 - 49 mL/hr. (2.0 -3.9 g ethanol/hr.) required intubation during the infusion, while the incidence of on-treatment intubation was 24% and 50% for patients receiving an initial IVE rate between 50 - 74 mL/hr. (4.0 – 5.8 g ethanol/hr.) and 75 -100 mL/hr. (5.9 – 7.9 g ethanol/hr.), respectively (p = 0.012).

Important differences were observed in patients receiving IVE for prophylaxis versus treatment (Table 5). Patients receiving IVE for treatment spent significantly more infusion time outside of goal CIWA score (p = < 0.001) and were administered larger daily volumes of IVE (p = 0.05). A non-significant increase in infusion time spent outside of goal SAS range and benzodiazepine requirements was also noted.

DISCUSSION

We identified that patients receiving IVE spent a majority of infusion time within goal SAS and CIWA range and required low doses of benzodiazepines. Indication for IVE and presence of mechanical ventilation are likely to be

Table 4. Sub-population analysis of initial IVE rate and surrogate efficacy and safety outcomes between mechanically ventilated vs. non-mechanically ventilated patients

	Not Mechanically Ventilated During IVE Infusion (n = 40)	Mechanically Ventilated During IVE Infusion (n = 29)	p - value
Percent of infusion time spent outside goal SAS score (n = 67 evaluable), median (IQR)	0 (0-5.1)	21.1 (9.9-58.0)	< 0.001
Above, median (IQR)	0 (0-5.1)	11.6 (3.8-28.3)	< 0.001
Below, median (IQR)	0 (0-0)	1.7 (0-23.2)	< 0.001
Lorazepam equivalent (mg/day), median (IQR)	0 (0-1.7)	2 (0.5-16.2)	0.002
Initial infusion rate, (g ethanol/hr.), median (IQR)	4.0 (3.4-5.5)	5.5 (4.0-6.3)	0.028
		On-treatment Intubation (n = 15)	
	4.0 (3.4 – 5.5)	5.9 (4.7-7.5)	0.006

CIWA = Clinical Institute Withdrawal Assessment SAS = Sedation and Agitation Score IVE = intravenous ethanol IQR = interquartile range
Data are reported as median (interquartile range)

Table 5. Sub-population analysis of IVE infusion data and surrogate efficacy and safety outcomes between patients receiving IVE for treatment vs. prophylaxis

	AWS Prophylaxis (n = 45)	AWS Treatment (n = 24)	p - value
ICU length of stay (hours), median (IQR)	218.4 (91.2 – 504.0)	192 (115.2 – 405.6)	0.632
Initial IVE rate (g ethanol/hr.), median (IQR)	4.7 (4.0 – 5.9)	4.3 (4.0 – 5.9)	0.923
Daily infused ethanol volume (mL), median (IQR)	956 (699 – 1201)	1212 (957 – 1328)	0.050
Duration of IVE infusion (hours), median (IQR)	77.8 (54.2 – 102.7)	82.1 (54.2 – 99.1)	0.960
Number of up-titrations, median (IQR)	0 (0 - 1)	0.5 (0 – 1.25)	0.204
Lorazepam equivalent (mg/day), median (IQR)	0.14 (0 – 2.09)	1.83 (0.19 – 4.90)	0.109
Percent of infusion time spent outside goal CIWA score (n = 34), median (IQR)	0 (0 – 3.7)	12.8 (8.6 – 21.5)	< 0.001
Percent of infusion time spent outside goal SAS score (n = 67), median (IQR)	2.4 (0 – 16.0)	9.5 (3.5 – 34.4)	0.081
Above, median (IQR)	1.7 (0 – 9.5)	8.3 (2.3 – 22.9)	0.025
Below, median (IQR)	0 (0 – 1.6)	0 (0 – 0)	0.67
Mechanical ventilation during infusion, n (%)	21 (46.7)	8 (33.3)	0.317
On treatment intubation, no./tot. possible (%)	9/33 (27.3)	6/22 (27.3)	> 0.999

AWS = alcohol withdrawal syndrome CIWA = Clinical Institute Withdrawal Assessment SAS = Sedation and Agitation Score ICU = intensive care unit IVE = intravenous ethanol IQR = interquartile range
Data are reported as n (%) or median (interquartile range)

confounders in any future comparative studies as these factors were associated with significant differences in benzodiazepine requirements and time spent within SAS and CIWA ranges. We reported a significant number of patients having IVE initiated despite exhibiting signs of withdrawal, which was inconsistent with our institution's guideline. Although a majority of patients received a dose of a benzodiazepine, median daily doses were low and a minority of patients required increases in infusion rates and experienced prophylaxis failure. However, the association between initial IVE infusion rate and on-treatment intubation, use in several patients with a history of cirrhosis or hepatitis, and the identification of several ICU admissions and central line placements that may have been avoided with an alternative AWS management strategy all indicate the use of IVE carries risk and poses an ethical dilemma. The use of IVE is even more questionable in patients with underlying liver disease. Concerningly, we reported several patients receiving IVE despite having a history of hepatitis or cirrhosis. Additionally, as the standard of care for managing AWS has shifted towards utilizing benzodiazepines and/or phenobarbital in a symptom triggered treatment approach, which is associated with both a decreased treatment time and reduced doses of GABAergic agents compared to fixed dosing schedules, the utility of any prophylactic AWS regimen was unclear [2,7,9,19-21].

Little contemporary data concerning IVE practices and patient outcomes exists. Evidence surrounding the efficacy of IVE for AWS prophylaxis is conflicting. A previously conduced retrospective study of 11 alcohol dependent ICU patients found that IVE prevented AWS in all cases [13]. A different retrospective review of ethanol dependent surgical ICU patients identified a 20% AWS prophylaxis failure rate with IVE. In the same study, a prospective examination of patient outcomes after protocolization of IVE noted that the failure rate decreased to 7% [14]. A review of 97 ICU and floor patients receiving IVE for prophylaxis reported a failure rate of 8% with an additional 26% of patients experiencing symptoms consistent with AWS. 54 percent of patients in that study also received a dose of a benzodiazepine [16]. An uncontrolled study of 22 alcohol dependent patients with thermal injuries found that IVE administered to achieve sub-intoxicating blood resulted in successful prevention of AWS symptoms in all patients [12]. However, another prospective observational study involving 32 alcohol dependent patients requiring ICU admission after elective surgery or surgery status post trauma found high rates of IVE prophylaxis failure with 41% of patients experiencing AWS symptoms [15]. A randomized controlled trial involving alcoholic dependent patients admitted to the ICU after tumor resection demonstrated no significant difference in outcomes including the incidence of development of AWS between patients randomized to receive IVE versus flunitrazepam-clonidine, chlormethiazole-haloperidol and flunitrazepam-haloperidol for AWS prevention [22]. A more recent randomized trial compared IVE to intravenous diazepam in fifty trauma patients and found high rates of successful AWS prophylaxis using a 4 day regimen in both groups with no significant difference between the two interventions in preventing withdrawal symptoms in susceptible patients. The study did observe that IVE was associated with less time in the goal sedation range compared to diazepam [11]. Extrapolation of the results from those studies to current practice is questionable due to their small sample sizes, heterogenous populations and outcomes and evolution of the standard of care of AWS.

We reported a higher percent of patients receiving benzodiazepines compared to other studies, but low overall daily benzodiazepine dose requirements and barbiturate use [16]. It is possible that IVE attenuated the need for other GABAergic agents in our patient population, but without a comparator group we are unable to make such determinations. Compared to other studies, we reported a higher percent of patients needing increases in IVE infusion and a similar rate of prophylaxis failure [11-16]. Other studies have reported improved outcomes and dosing consistency with the implementation of a guideline that includes a structured dosing strategy. However, despite having had an institutional guideline in place, we observed inconsistent practices in IVE dosing, patient selection and indication [14]. It should be emphasized that our study differs from these previous studies in design, patient population, and time period related standards for alcohol withdrawal management. Therefore, inferences made by comparing and contrasting our data with those of previous works should be done cautiously.

LIMITATIONS

Our study has several limitations. It should be considered that our study period spans over 7 years. During this time, standards of practice for managing AWS and sedation in critically ill patients changed. Our institutional IVE guideline did not offer specific recommendations for infusion titration or use of adjunctive AWS agents. As a result, IVE infusion and AWS management practices were not standardized and it is not clear to what degree the inter-provider differences in these practices led to patient outcomes. Most notably, as our data is retrospective in nature, we can only comment on associations between specific data points in this cohort of patients as there was no control group managed without IVE. As a majority of patients were critically ill and had undergone thoracic surgery, it is unclear to what degree poorly controlled withdrawal symptoms versus unaccounted factors such as ventilator compliance were responsible for the increased benzodiazepine requirements and increased infusion time spent outside goal SAS range observed in mechanically ventilated patients. Likewise, although we found a significant association between higher initial IVE rate and the incidence of on-treatment intubation, it is not clear if the higher incidence of intubation was related to higher initial rates of IVE, refractory withdrawal symptoms, volume overload due to IVE and other fluids, or was multifactorial. We speculate that a high quality comparative retrospective study on this topic would be difficult to undertake. The population of patients that received IVE at our institution was heterogeneous due to hospital admission rules,

indication for IVE, and the need for mechanical ventilation. Obtaining a homogenous sample that excludes patients with known confounders would likely result in a small patient population that would not be conducive for a robust analysis.[1]

CONCLUSION

Patients spent a majority IVE infusion time within goal CIWA and sedation range and received low doses of benzodiazepines. The presence of mechanical ventilation and IVE indication should be accounted for as confounders in any future study as these factors appeared to influence patient outcomes related to benzodiazepine requirements and SAS scores. We observed inconsistent practices in terms of indication for IVE use and dosing. Most patients required additional GABAergic agents, adjunctive AWS treatments or an increase in ethanol infusion rate during treatment. An association between initial IVE rate and on-treatment intubation was identified.

Our results help to further define and clarify the risks and benefits of utilizing IVE for AWS management. Until data from prospective, randomized controlled trials are available it will remain unclear if IVE confers any benefit over standard therapies for managing AWS in critically ill patients likely to experience withdrawal.

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