Impact of a national propofol shortage on duration of mechanical ventilation at an academic medical center

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Objective: **To measure the impact of a national propofol shortage on the duration of mechanical ventilation.**

Design: **Before–after study.**

Setting: **Three, noncardiac surgery, adult intensive care units at a 320-bed academic medical center.**

Patients: **Consecutive patients requiring mechanical ventilation ≥48 hrs, administered a continuously infused sedative ≥24 hrs, extubated, and successfully discharged from the intensive care unit were compared between before (December 1, 2008 to May 31, 2009) and after (December 1, 2009, to May 31, 2010) a propofol shortage.**

Intervention: **None.**

Measurements and Main Results: **Sedation drug use and common factors affecting time on mechanical ventilation were collected and if found either to differ significantly ($p \leq .10$) between the two groups or to have an unadjusted significant association ($p \leq .10$) with time on mechanical ventilation were included in a multivariable model. The unadjusted analyses revealed that the median (interquartile range) duration of mechanical ventilation increased from 6.7 (9.8; n = 153) to 9.6 (9.5; n = 128) days ($p = .02$). Fewer after-group patients received ≥24 hrs of continuously infused propofol (94% vs. 15%, $p < .0001$); more received ≥24 hrs of continuously infused lorazepam (7% vs. 15%, $p = .037$) and midazolam (30% vs. 81%, $p < .0001$). Compared with the before group, the after group was younger, had a higher admission Acute Physiology and Chronic Health Evaluation II score, was more likely to be admitted by a surgical service, have acute alcohol withdrawal, and be managed with pressure-controlled ventilation as the primary mode of mechanical ventilation. Of these five factors, only the Acute Physiology and Chronic Health Evaluation II score, admission service, and use of a pressure-controlled ventilation affected duration of mechanical ventilation across both groups. Although a regression model revealed that Acute Physiology and Chronic Health Evaluation II score ($p < .0001$), admission by a medical service ($p = .009$), and use of pressure-controlled ventilation ($p = .02$) each affected duration of mechanical ventilation in both groups, inclusion in either the before- or after-propofol shortage groups (i.e., high vs. low use of propofol) did not affect duration of mechanical ventilation ($p = .35$).**

Conclusions: **An 84% decrease in propofol use in the adult intensive care units at our academic institution as a result of a national shortage did not affect duration of mechanical ventilation. (Crit Care Med 2012; 40:000–000)**

Key Words: before–after study; benzodiazepine; critical care; dexmedetomidine; drug shortage; intensive care unit; lorazepam; mechanical ventilation; midazolam; outcomes; prescribing patterns; propofol; sedation

Propofol, an intravenous general anesthetic agent, is the most frequently used sedative in American intensive care units (1, 2). Compared with benzodiazepines such as midazolam or lorazepam, propofol, with its rapid onset and offset, results in a faster recovery from sedation and a shorter duration of mechanical ventilation (3–6). These advantages persist even when benzodiazepines are administered on a scheduled intermittent basis and therapy is interrupted on a daily basis to maintain the patient in an arousable state (6).

In October 2009, two of the three U.S. manufacturers of propofol recalled their entire supply of propofol (7). Hospira Pharmaceuticals had found particulate matter in one or more batches and Teva Pharmaceuticals had found microbial contamination. In May 2010, Teva Pharmaceuticals permanently discontinued production. Hospira Pharmaceuticals resumed production in January 2011. APP Pharmaceuticals, the smallest supplier of propofol at the time of the Hospira and Teva recalls, became the sole U.S. supplier for >1 yr resulting in persistent propofol shortages at many U.S. hospitals.

This shortage led our 320-bed academic medical center to restrict use of propofol to patients who had an anticipated short duration of therapy (e.g., undergoing a procedure) or who required frequent neurologic assessment. Medical and surgical intensive care unit (ICU) clinicians were therefore forced to increase their use of benzodiazepine-based sedation regimens despite extensive literature

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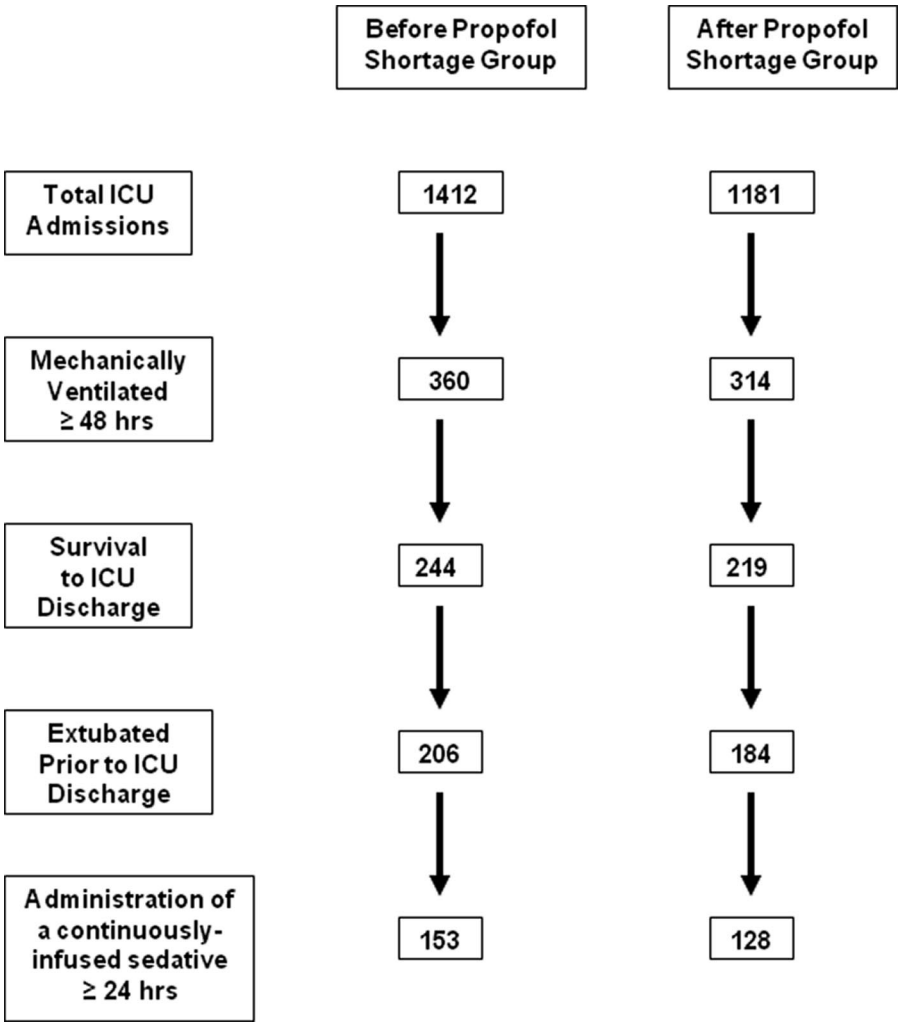

Figure 1. Patient enrollment and exclusion in each group. Intensive care unit, *ICU*.

demonstrating that use of a benzodiazepine-based sedation regimen leads to slower sedation recovery and a longer duration of mechanical ventilation. Despite the extent and persistence of this shortage and substantial concern among clinicians and hospitals surrounding it, there are little data evaluating its impact on patient outcomes (7, 8).

Duration of mechanical ventilation is frequently evaluated not only in controlled studies, but also at individual institutions when the impact of new ICU practices or quality assurance initiatives are evaluated (6, 9–11). Furthermore, hospital administrators often track duration of mechanical ventilation over time because of the important effect it can have on patient throughput and ICU capacity (12).

We therefore sought to measure the impact of the national shortage of propofol on the duration of mechanical ventilation for consecutive adults admitted to noncardiac surgery ICUs at our academic institution. In addition, we explored the effect on the comparison between time periods of taking into account patient-level factors known to influence duration of mechanical ventilation.

METHODS

This retrospective before–after propofol shortage analysis was conducted at Tufts Medical Center and approved by the Tufts institutional review board who waived the need for informed consent. Consecutive patients admitted to the three ten-bed, adult, noncardiac surgery ICUs during a period before the propofol shortage or a period after the shortage were enrolled if they were mechanically ventilated ≥48 hrs, successfully extubated, and then discharged from the ICU and administered ≥24 hrs of continuously infused lorazepam, midazolam, propofol, and/or dexmedetomidine during the period of intubation. Patients who received a tracheostomy were included in the analysis only if they did not require mechanical ventilatory support at the time of ICU discharge. Patients who died while mechanically ventilated or underwent a terminal wean from mechanical ventilation were excluded from the analysis. For patients with one or more ICU admission during a study period, only the first ICU admission was included in the analysis.

Because the shortage of propofol became persistent at our institution during October 2009 and started to intermittently improve in the summer of 2010, we defined the "after" period as December 1, 2009, through May 31, 2010. To minimize confounding of seasonal variation with the comparison between the before and after periods, the "before" group comprised patients who were admitted to the same three study ICUs between December 1, 2008, and May 31, 2009. Patients who were initiated on mechanical ventilation but not yet extubated during either of these two periods were included in the analysis.

Study patients were first identified using the department of respiratory therapy's ICU database (Microsoft Access, Seattle, WA). Using the institutional patient database (Soarian; Siemens, Malvern, PA), those patients not surviving to ICU discharge were excluded. We also excluded patients who were not found in a report from the institutional pharmacy database (Siemens) of all ICU patients administered a continuous infusion of dexmedetomidine, lorazepam, midazolam, or propofol for ≥24 hrs.

Nonmedication-related factors that either have been proven or are suspected to influence the duration of mechanical ventilation and that could be retrieved from the electronic patient record were extracted for all patients (13–21). These included: age, admission Acute Physiologic and Chronic Health Evaluation II score, admitting service (i.e., medical vs. surgical), presence at admission of the acute respiratory distress syndrome or sepsis (vs. other primary causes for ICU admission), presence of acute alcohol withdrawal at admission, the admission PaO_2/FIO_2 ratio, presence of renal failure (a serum creatinine ≥1.8 mg/dL at admission), and use of pressure-controlled ventilation as the most frequent mode of mechanical ventilation. At our institution, assist-control or synchronous intermittent mandatory ventilation are the most frequent modes of mechanical ventilation used. Pressure-controlled ventilation is used when respiratory failure is so severe that conventional modes of ventilation (i.e., assist-control or synchronous intermittent mandatory ventilation) fail to alleviate hypoxemia or excessive airway pressure.

Although the admitting service is not a well-established influence on duration of mechanical ventilation, we chose to include it in our analysis because of the suspected variability in weaning practices between medical and

Table 1. Use of sedation, opioid, neuromuscular blocker, and antipsychotic therapy between the before- and after-propofol shortage groups[a]

Parameter[b]	Before Shortage (n = 153)	After Shortage (n = 128)	p
Patients administered each continuous sedation infusion ≥24 hrs, %			
Dexmedetomidine	9	27	<.0001
Lorazepam	7	14	.04
Midazolam	36	73	<.0001
Propofol	94	15	<.0001
Duration of all continuous sedation infusions			
Days	6 (3–12)	5 (3–9)	.02
As a percent of time on mechanical ventilation	94 (68–111)	59 (35–82)	<.0001
Duration, days, of each sedation infusion (among those patients administered it)			
Dexmedetomidine	1.3 (0.5–2.5)	2.8 (1.5–4.5)	.012
Lorazepam	3.0 (1.5–4.0)	4.50 (2.5–7.5)	.347
Midazolam	4.0 (2.5–9.0)	4.0 (2.5–8.0)	.446
Propofol	4.5 (3.0–8.0)	4.0 (2.0–9.5)	.763
Midazolam equivalents of sedation infusion administered, mg			
Average (for all patients in each group)	1117 (575–2200)	450 (200–1247)	<.0001
Average (for only those patients administered it)			
Dexmedetomidine	68 (14–109)	81 (41–216)	.278
Lorazepam	787 (485–1817)	1090 (606–2059)	.387
Midazolam	400 (200–1050)	400 (200–750)	.251
Propofol	990 (511–1820)	830 (351–2267)	.716
Average midazolam equivalent rate of sedation infusions administered, mg/hr	7.6 (5.3–11.2)	4.2 (2.8–6.3)	<.0001
Continuous opioid infusion administered ≥24 hrs, %	87	82	.47
Neuromuscular blocker infusion administered ≥24 hrs, %[c]	5	13	.01
Scheduled antipsychotic administered ≥24 hrs, %	17	25	.23

[a]Patients frequently received more than one continuously infused sedative over the course of their intensive care unit stay; [b]reported as median (interquartile range of 25th to 75th percentile) unless otherwise noted; [c]neuromuscular blocker information was missing for four patients in the "after" group.

surgical services. Two months from the start of the propofol shortage group data collection period, an institutional daily awakening–spontaneous breathing protocol was implemented in the three study ICUs. Although daily awakening–spontaneous breathing protocols have been shown to reduce oversedation and facilitate extubation, we did not include it in our analysis given that it was not in use during the before-shortage period, it was implemented partway through the after period, and initial clinician compliance to it after it was implemented was expected to be low (7, 22–24).

Data on continuously infused sedatives, opioids, and neuromuscular blockers, and scheduled antipsychotics that were administered was obtained from the institutional pharmacy database: the total days and total amount (in milligrams or micrograms) of each continuously infused sedative (i.e., dexmedetomidine, lorazepam, midazolam, or propofol) that was administered ≥24 hrs was recorded. The patient's average infusion rate of each sedative was calculated by dividing the total amount of each sedative administered by the hours it was administered. Because many patients received more than one continuously infused sedative, we converted amounts to midazolam equivalents using the following conversion: midazolam 5 mg/hr = lorazepam 3 mg/hr = propofol 200 mg/hr = dexmedetomidine 74.1 μg/hr. (25, 26). Sedative, opioid and neuromuscular blocker, and antipsychotic therapy administered on an "as-needed" basis is not captured electronically at our institution and thus was not incorporated in the analysis.

All drug and patient data are summarized as either percent, mean ± SD, or in cases of skewed distribution, as median (interquartile range), and compared between the before- and after-groups using a chi-squared test, Student's t test, or the Mann-Whitney U test. Comparisons of factors between the before and after groups were considered significant for inclusion in the building of the multivariable model of days of mechanical ventilation if the unadjusted association had a p value of ≤ .10. The separate relationships between days of mechanical ventilation and each relevant factor was also examined using Spearman rank correlations, the Student's t test, or the nonparametric Kruskal-Wallis test. Variables having unadjusted p values of ≤ .10 were considered as potentially associated with the duration of mechanical days and were also included in the multivariable model process.

The distribution of the duration of mechanical ventilation was right-skewed and thus transformed to a logarithmic base 10 scale for the linear regression analysis. A multivariable linear regression model was built using a stepwise selection process. The first variable included in the model, and forced into all subsequent models, was an indicator variable with a value of "1" to denote the "after" period and a value of "0" to denote the "before" period. Again, all other variables with unadjusted associations with the period (i.e., after vs. before) or the days of mechanical ventilation were considered as candidates to step into the model. The Schwartz Bayesian information criteria in conjunction with clinical judgment was used to guide the choice of the final model. The GLMSelect procedure of SAS 9.2 for Windows (Cary, NC) was used for the model-building process and to observe the impact of each added variable on the Schwartz Bayesian information criteria. Residuals from the final model were reviewed to confirm that continuous variables included in the model were correctly specified. Unless otherwise stated, a p value ≤ .05 signified statistical significance. All analyses were done using SAS 9.2 for Windows.

RESULTS

Figure 1 shows the number of patients admitted to the three study ICUs during the before and after periods and the number of patients removed from the analysis by the exclusion criteria. A total of 281 patients are reported on in this article. The after group (n = 128) had a longer median (interquartile range) duration of mechanical ventilation than the before group (n = 153): 9.6 (9.5) vs. 6.7 (9.8) days (p = .02). Fewer after group patients received ≥24 hrs of continuous propofol (94% vs. 15%, p < .0001) and more received ≥24 hrs of continuous lorazepam (7% vs. 14% high-frequency oscillatory ventilation, p = .04) midazolam (36% vs. 73%, p < .0001), or dexmedetomidine (9% vs. 27%, p < .001) (Table 1). The after-propofol shortage group had a shorter total duration of continuously infused sedation, received fewer total midazolam equivalents of sedation, and was administered sedation at a lower average infusion rate. Although the administration of ≥24 hrs of continuously infused

Table 2. Comparison of unadjusted factors that could affect duration of mechanical ventilation between the before- and after-propofol shortage groups and their relationship to days of mechanical ventilation[a]

Parameter	Before Shortage (n = 153)[b]	After Shortage (n = 128)[b]	*p* Value Between Before and After Groups	*p* Value for Relationship With Duration of Mechanical Ventilation
Age, yrs	62.1 ± 15.9	57.0 ± 16.7	.01	.87
Male (%)	64.4	63.3	.72	—
Medical service, %	78.4	64.0	.008	.1
Acute Physiologic and Chronic Health Evaluation II score[b]	19 ± 5.7	20.1 ± 6.3	.1	.0001
Worse PaO_2/FIO_2 ratio in first 24 hrs after intensive care unit admission[b]	250 (175–352)	240 (180–354)	.56	—
Primary reason for intensive care unit admission, %				—
Respiratory (nonacute respiratory distress syndrome)	25	22	.79	
Sepsis/acute respiratory distress syndrome	22	17	.26	
Cardiac	20	15	.33	
Neurologic	17	19	.63	
Toxic/metabolic	6	5	.86	
Gastrointestinal	5	9	.41	
Trauma	4	6	.68	
Other	1	7	—	
Active alcohol withdrawal, %	4.6	9.6	.09	.76
Admission serum creatinine, mg/dL[b]	1.11 (0.8–1.99)	1.09 (0.7–1.77)	.35	—
Pressure-controlled ventilation the most frequent ventilator mode, %	4.6	9.3	.07	.05
Use of pressure-controlled ventilation ≥24 hrs, %	20	18.4	.6	—

[a]Reported as either mean ± SD or median (interquartile range of 25th to 75th percentile); [b]Acute Physiologic and Chronic Health Evaluation II score was missing in one patient in the after group; worse PaO_2/FIO_2 ratio and serum creatinine missing in three patients in the after group.

opioids and scheduled antipsychotics was similar in the two groups, the after group was more likely to receive continuous neuromuscular blocker therapy.

Compared with the before-shortage group, the after-shortage group was younger ($p = .01$), were less likely to be admitted to a medical service ($p = .008$), had a slightly higher admission Acute Physiologic and Chronic Health Evaluation II score ($p = .1$), was more likely to be admitted with active alcohol withdrawal ($p = .09$), and was more likely to receive pressure-controlled ventilation as the most frequent ventilatory mode ($p = .07$) (Table 2). The other demographic and clinical factors were similar in the two groups. Three factors were found to have unadjusted associations ($p \leq .10$) with the duration of mechanical ventilation: admission to a medical (vs. surgical) service ($p = .10$), admission Acute Physiologic and Chronic Health Evaluation II score ($p = .0001$), and use of pressure-controlled ventilation as the most frequent mode of mechanical ventilation ($p = .07$) (Table 2). Fewer than 2% of the patients were missing data for any variable with details of missing data provided in Tables 1 and 2.

The distribution of the duration of mechanical ventilation in days was right-skewed and thus transformed to a logarithmic base 10 scale for multivariable linear regression analyses.

The adjusted multivariable linear regression model we built, using log10 days of mechanical ventilation as the dependent variable, revealed that admission to a medical service (adjusted $p = .009$), higher admission Acute Physiologic and Chronic Health Evaluation II score (adjusted $p < .0001$), and use of pressure-controlled ventilation as the most frequent mechanical ventilation mode (adjusted $p = .02$) each were all associated with longer duration of mechanical ventilation across the two groups (Table 3). However, when the indicator variable that defined the after vs. before propofol shortage periods was forced into this model (i.e., to estimate the adjusted impact of the propofol shortage on duration of mechanical ventilation), it failed to show statistical significance (adjusted $p = .35$).

From the parameter estimates presented in Table 3, these findings can be interpreted as follows: 1) without adjustment, the estimated geometric mean duration of mechanical ventilation was 20% longer in the "after-shortage" compared with the "before-shortage" period ($p = .05$); and 2) when adjusted for covariates that affected duration of mechanical ventilation, the duration of mechanical ventilation increased by approximately 7% ($p = .35$) demonstrating that a large decrease in propofol use because of the national shortage had little influence on days of mechanical ventilation in the noncardiac ICUs at our institution.

DISCUSSION

Over the past decade, the United States has seen a large increase in the number of manufacturer shortages of intravenous medications that are frequently used in critical care settings (7, 27, 28) Substitution of an intravenous medication from a different pharmacologic class may compromise therapeutic efficacy and place patients at increased risk for adverse effects that may not have

Table 3. Estimated difference in days of mechanical ventilation between the after- and before-propofol shortage periods: Unadjusted and multivariable adjusted linear regression models of $\log_{10}$ days (n = 277 subjects)[a]

Variable	Unadjusted Model (R^2 = 0.012)			Adjusted Model (R^2 = 0.103)		
	Parameter Estimate	SE	*p*	Parameter Estimate	SE	*p*
Intercept	0.89	0.03	<.0001	0.72	0.07	<.001
Before propofol shortage vs. after propofol shortage[b]	0.08	0.04	.05	0.03	0.04	.35
Medical service				−0.12	0.05	.009
Acute Physiologic and Chronic Health Evaluation II score				0.01	0.003	<.0001
Pressure-controlled ventilation the most frequent mode of mechanical ventilation				0.19	0.08	.02

[a]The total sample size in the study was 281. Two subjects were excluded from these regression models because high-frequency oscillating ventilation. Two others were excluded because they were missing the mode of ventilation or the Acute Physiologic and Chronic Health Evaluation II score; [b]coefficients show the estimated difference in the $\log_{10}$ days of mechanical ventilation between the before and after periods. Positive values indicate the average duration of mechanical ventilation is higher in the "after" compared with the "before" periods. The geometric mean was approximately 20% higher in the after group (10^0.08). After adjusting for medical service, Acute Physiologic and Chronic Health Evaluation II, and ventilator mode, the estimated increase in the geometric mean of the "after" vs. "before" periods was only approximately 7% (10^0.03) longer.

occurred had the preferred medication been available. Our study is the first to attempt to evaluate the impact of a national shortage of an intravenous medication on the outcome of patients admitted to the ICU. Specifically, we found that a national shortage of propofol resulted in an 84% decrease in the use of propofol and close to a 100% increase in the use of continuously infused benzodiazepines and increased the duration of mechanical ventilation, on average, by 2 days. However, factors known or suspected to influence the duration of mechanical ventilation accounted for the observed difference in duration. Our analysis also highlights the limitations of analyzing an outcome like days on mechanical ventilation without taking potential influential factors into account.

How can we conclude that a large decrease in propofol use did not prolong the duration of mechanical ventilation when multiple randomized controlled trials have demonstrated that the use of benzodiazepines is associated with a longer duration of mechanical ventilation than use of propofol? (3–6). First, the results of randomized controlled trials frequently cannot be replicated outside of the controlled environment of a study (29). Although implementation of the daily awakening–spontaneous breathing protocol during the postshortage evaluation period may have accounted, in part, for the shorter time of continuous sedation and the lower infusion doses, a recent analysis of our daily awakening–spontaneous breathing protocol practices found that compliance to daily awakening was <50% and that its use did not reduce ventilator days (30).

With controlled trials demonstrating that use of dexmedetomidine is associated with a more ventilator-free days than with continuous benzodiazepine therapy, it remains unclear why our analysis found time on mechanical ventilation was longer in the after group when the proportion of patients receiving dexmedetomidine during this period was nearly three times greater (26, 31, 32). It is possible that dexmedetomidine was administered differently at our institution than in those studies. Although the greater use of neuromuscular blocker therapy in the after-shortage group may reflect the lower amount of sedation administered to this group, it could also reflect the greater number of patients who required pressure-controlled ventilation. However, from the results of a recent randomized controlled trial demonstrating that patients with severe acute respiratory distress syndrome who receive early neuromuscular blocker therapy had significantly more ventilator-free days compared with placebo, one would have expected patients in the after group to have a shorter duration of mechanical ventilation (33).

Our study has a number of potential limitations. We cannot exclude the possibility that the large decrease of propofol use that occurred as a result of the shortage did not have some effect on the duration of mechanical ventilation. However, this effect is likely very small given that three, nondrug-related factors were found to account for most of the difference in duration of mechanical ventilation between the two groups. Although other factors have been reported to affect duration of mechanical ventilation (e.g., patient ventilator dysynchrony, critical illness polyneuropathy), most are not easily captured in a retrospective analysis such as ours (13–20, 34). The amount of "as-needed" sedation was not collected for either group.

Although delirium may increase the duration of mechanical ventilation, the number of patients who developed delirium in the study was not available electronically and thus was not collected (35). However, because both delirium screening and the same restrictive policy surrounding antipsychotic use were in place in each ICU during both study periods, the similar use of scheduled antipsychotic therapy in the two groups suggests that the incidence of delirium was similar as well. Although weaning strategies were standardized in each ICU service at our institution, they are not standardized across the institution. Furthermore, the completion and success of weaning efforts are generally poorly documented, so we were not able to retrieve these data. Lastly, our analysis also did not seek to measure the impact of the propofol shortage on safety-related outcomes such as unplanned extubations or the incidence of medication-related adverse events such as the propofol-related infusion syndrome (36, 37).

This study also highlights the fact that numerous factors can affect the duration of mechanical ventilation in the ICU patient, that the effects of individual factors on duration are challenging to elucidate, and most importantly that comparing the duration of mechanical ventilation between two patient cohorts using only univariate analysis may lead to misleading or false conclusions (9, 11). Hospitals that track duration of mechanical data over time for administrative purposes or use this end point to measure the impact of

new quality assurance initiatives should recognize the potential limitations of univariate methods. At the very least, clinicians should ensure that comparative groups are well matched on factors that can affect time on ventilation.

In conclusion, our study showed that a national shortage of propofol did not have a notable effect on the duration of mechanical ventilation among noncardiac ICU patients at our academic institution. However, in an era of ever-increasing ICU drug shortages, future research is required to determine those factors that affect the supply of intravenous medications that are routinely used in the ICU, evaluate the impact of proposed legislation focused on alleviating this issue, and measure the impact of any ICU medication shortage on patient outcome (38).

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