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Propranolol As an Anxiolytic to Reduce the Use of Sedatives for Critically Ill Adults Receiving Mechanical Ventilation (PROACTIVE): An Open-Label Randomized Controlled Trial

James Downar, MD, MHSc[1,2,3]
Julie Lapenskie, MSc[2]
Salmaan Kanji, PharmD[3]
Irene Watpool, BSc[3]
Jessica Haines, BScN[3]
Uzma Saeed, BSc[4]
Rebecca Porteous, BSc[3]
Nadia Polskaia, PhD[2]
Lisa Burry, PharmD, PhD[5]
Shuhira Himed, BSc[4]
Koby Anderson, BSc[2]
Alison Fox-Robichaud, MD, MSc[4,6]

OBJECTIVES: Surges in demand for sedatives for mechanical ventilation during the COVID-19 pandemic caused shortages of sedatives globally. Propranolol, a nonselective beta-adrenergic blocker, has been associated with reduced agitation and sedative needs in observational studies. We aimed to test whether propranolol could reduce the dose of sedatives needed in mechanically ventilated patients.

DESIGN: Open-label randomized controlled trial.

SETTING: Three academic hospitals.

SUBJECTS: Any nonparalyzed patient receiving mechanical ventilation and requiring high-dose sedatives.

INTERVENTIONS: Enteral propranolol 20–60 mg every 6 hours titrated to effect in the intervention group; all participants received protocol-titrated sedation with propofol or midazolam.

MEASUREMENTS AND MAIN RESULTS: Mean change in 24 hours dose of sedative from baseline to day 3, proportion of sedation scores within target, and occurrence rate of adverse events. We enrolled a planned 72 patients between January 2021 and October 2022. Sixty-nine percent were male with a mean (SD) age of 54 years (15.91 yr). Most were admitted for COVID or non-COVID pneumonia. Intervention participants received propranolol for a mean of 10 days (mean daily dose, 90 mg). There was a significantly larger decrease in sedative dose from baseline (54% vs. 34%; $p = 0.048$) and more sedation assessments within target range (48% vs. 35%; $p < 0.0001$) in the intervention group compared with controls. There were no differences in mortality or adverse events.

CONCLUSIONS: Propranolol is an inexpensive drug that effectively lowered the need for sedatives in critically ill patients managed in the COVID-19 pandemic. Propranolol may help preserve limited supplies of sedatives while achieving target sedation.

KEYWORDS: beta-blocker; critical care; drug conservation; drug repurposing; Richmond Agitation-Sedation Scale

Critically ill patients often require sedation to tolerate mechanical ventilation, with guidelines recommending dexmedetomidine and propofol as first-line sedatives (1). Surges in demand for mechanical ventilation during the COVID-19 pandemic, resulted in shortages of propofol in Canada, the United States, and other parts of the world (2, 3). Dexmedetomidine is not commonly used for deep sedation, and its use is often limited due to high costs. Benzodiazepines (e.g., midazolam) can be used for sedation in the ICU, but they are associated with higher mortality in sepsis, higher occurence rate of delirium,

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KEY POINTS

Question: Does enteral propranolol reduce the dose of sedatives needed in mechanically ventilated patients?

Findings: Enteral propranolol significantly reduces the need for IV sedatives in mechanically ventilated patients without an apparent increased risk of adverse events.

Meanings: Enteral propranolol is a cheap and plentiful medication that may help reduce the sedative doses needed in mechanical ventilation. Our findings may be helpful in future pandemics when sedative supplies run low or in resource-limited settings.

and longer length of stay in the ICU (1, 2), and were also in shortage throughout the pandemic (4).

In critically ill patients, agitation and delirium are often driven by hyperactivity in the sympathetic nervous system, as neurotransmitters such as norepinephrine are produced or administered to increase blood pressure and heart rate (HR). The locus ceruleus (LC) provides the majority of brain norepinephrine (5, 6), and LC adrenergic input to the medial septal area and medial preoptic area of the forebrain mediates arousal (5, 7–10). Propranolol, a nonselective beta-adrenergic blocker with good penetration across the blood brain barrier (11), is approved for treating hypertension, angina, arrhythmias, migraines, and pheochromocytoma in Canada (12). It is also used off-label to treat anxiety disorders such as post-traumatic stress disorder (PTSD) (13). As a lipophilic molecule, propranolol crosses the blood-brain barrier and can block ability of the LC to activate the forebrain, similar to alpha-2 agonists like dexmedetomidine (5, 14). Propranolol use has been associated with reduced agitation, length of stay, and potential mortality in patients with traumatic brain injury (15–19) and improved length of stay in severely burned patients (17). We previously published a retrospective study that found the initiation of propranolol was associated with a substantial reduction in sedative doses while maintaining the desired sedation (20).

Given the potential for pandemic-related surges in mechanical ventilation to exhaust our supply of sedatives, we conducted a prospective randomized study to determine whether the use of propranolol, an accessible and inexpensive enteral medication, could substantially reduce the sedative requirements of patients receiving mechanical ventilation. Our secondary objectives were to assess whether the use of propranolol improves patient-centered or patient-level outcomes such as delirium occurrence rate, ICU or hospital length of stay, mortality, or direct drug costs.

METHODS

Design

Multisite, open-label, parallel-arm randomized controlled trial (RCT).

Trial Registration

ClinicalTrials.gov registration number NCT04467086.

Sites

Three quaternary academic medical-surgical ICUs in Ontario, Canada (The Ottawa Hospital—General Site, The Ottawa Hospital—Civic Site, and Hamilton General Hospital) including approximately 180 level 3 critical care beds that account for 2500–3000 annual admissions requiring mechanical ventilation.

Eligibility Criteria

Adult patients anticipated to require mechanical ventilation greater than 48 hours who had: 1) a Richmond Agitation-Sedation Scale (RASS) (21) sedation target that was anticipated by the admitting physician to be stable greater than 48 hours and 2) minimum sedative infusion doses of either propofol greater than or equal to 1.5 mg/kg/hr for more than 24 hours or midazolam greater than or equal to 3.0 mg/hr for more than 24 hours. Patients were excluded if they required neuromuscular blocking agents at the time of enrollment; if they had any known contraindication to beta-blockers (e.g. asthma, first-, second-, or third-degree heart block with no permanent pacemaker, congestive heart failure with ejection fraction < 20%, or bradycardia [HR < 60 beats/min (bpm) at baseline]); hypotension requiring norepinephrine greater than 0.15 mcg/kg/min, epinephrine greater than 0.15 mcg/kg/min, dopamine greater than 22.5 µg/kg/min,

vasopressin greater than 0.06 U/min, phenylephrine greater than 2.0 μg/kg/min, or receiving 3 or more vasopressors regardless of dose; pregnancy or lactation; documented allergy to propranolol or tablet ingredients; inability to administer enteral medication; or receiving digoxin, diltiazem, or verapamil. Patients on chronic beta-blockers were eligible for enrollment; patients allocated to the intervention arm had their beta-blocker replaced with propranolol. Control patients already receiving a beta-blocker would continue it at the treating team's discretion.

Randomization

Participants were randomized (1:1 allocation) by site using a permeated block design with a fixed block size of four.

Intervention

Patients randomized to the intervention arm received propranolol enterally at a starting dose of 20 mg every 6 hours for two to four doses. They were then reassessed for titration every 24 hours (± 6 hr) at 10 mg dose increases to a maximum of 60 mg every 6 hours. Patients enrolled with HR 60–69 bpm received the starting dose of 20 mg propranolol to initiate the intervention, but this dose was not increased until HR was greater or equal to 70 bpm.

Daily study drug dose titration was guided by both sedation scores and hemodynamic markers indicative of the expected sympatholysis from propranolol. Downward titration in open label sedatives could continue until a minimum level of sedative infusion was reached (propofol < 0.5 mg/kg/hr or midazolam < 1.0 mg/hr). Admitting teams were instructed at each sedation assessment to determine if the sedation target could be achieved with lower doses of IV sedatives provided any of the following conditions were met: 1) HR less than 70 bpm, 2) mean arterial pressure (MAP) less than 70 mm Hg, or 3) norepinephrine or equivalent vasopressor dose increase to greater than 0.15 μg/kg/min. To promote a consistent and safe approach to simultaneously titrating an IV and an oral sedative (both of which have hemodynamic effects), the protocol recommended daily upward titration of propranolol (at the discretion of the admitting team) if none of the above conditions were met.

Control

Patients received open label sedatives titrated to a RASS target specified by the treating team, with instructions to regularly attempt to wean sedation as tolerated.

Randomization and Blinding

Participants were randomized using permeated block randomization (four-patient blocks) on a web-based platform, stratified by site to account for local variability in sedative practices. Participants and substitute decision-makers were blinded to assignment; clinical teams were not, due to the impracticality of placebo and need to modify standard responses to hypotension and bradycardia (**Appendix**, http://links.lww.com/CCM/H628, for detailed justification). Outcome assessors were study personnel and could not be blinded, as they collected information about medications administered (including propranolol).

Outcomes

The primary outcome was the change in total daily dose of primary sedative from baseline to study day 3. Secondary outcomes included the proportion of sedation scores within target range; proportion of patients whose sedative requirements on study day 3 were at or below the minimum level (propofol 0.5 mg/kg/hr or midazolam 1 mg/hr); change in total 24 hours dose of opioids from baseline to study day 3 (in parenteral morphine equivalents); and occurrence rate of adverse events, ICU and hospital length of stay, and occurrence rate of delirium.

We assessed safety by recording all unexpected and related (possibly or probably) adverse events. We also recorded expected adverse events from beta-blockers: bradycardia (HR < 50 or requiring intervention); hypotension (MAP < 60 requiring new vasopressor agents or an increase of > 0.1 μg/kg/min of norepinephrine or epinephrine from baseline persisting more than 2 hr after reducing sedative doses); clinically important bronchospasm requiring the initiation of bronchodilator therapy or a change in mechanical ventilation settings; or new electrocardiogram conduction delays.

Sample Size

We calculated our sample size based on the assumption that, to play a meaningful role in reducing the need

for sedatives, we would need to see at least a moderate effect size (0.5) for propranolol. To have 80% power to detect this difference, we would need 64 participants (32 per arm). Allowing for a 10% dropout rate, we aimed to enroll 72 patients.

Analysis

We followed an intent-to-treat approach for all non-sedative outcomes and a modified intent-to-treat analysis for sedative outcomes. For sedative outcomes, patients who were paralyzed during the outcome timeframe, were switched to palliative sedation for end-of-life care or died before day 3 (primary outcome timeframe) were excluded. There were two patients receiving methadone who were excluded from opioid outcomes analysis because of challenges determining equivalency to parenteral morphine.

We conducted an independent sample *t* test or Mann-Whitney *U* test, as appropriate, to compare mean changes in sedative doses in the intervention vs. control group. Proportion of RASS assessment within, below, or over target were analyzed using a Z test. For all secondary outcomes, mean and median comparisons between groups were performed using the Mann-Whitney *U* test and Mood's median test, respectively. Outcomes calculated as proportions were compared using Fisher exact test.

All statistical tests were two-sided and significance set at *p* value of less than 0.05. Levene's test for homogeneity of variance and Shapiro-Wilk test were used to test for assumptions of independence of variance and normality, respectively. Statistical analyses were performed using R software (Version R 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) and Excel (Microsoft 365, Version 2308; Microsoft, Redmond, WA).

Ethics

This trial was approved by the Ottawa Health Sciences Network Research Ethics Board through Clinical Trials Ontario (Project ID No. 3208; Title: Propranolol as an anxiolytic to reduce the use of sedatives for critically ill adults receiving mechanical ventilation: an open-label randomized controlled trial. (PROACTIVE); Initial Approval January 21, 2021) for both participating centers. An independent Data Safety Monitoring Board reviewed the safety endpoints after 21 and 54 participants were enrolled. All study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975.

RESULTS

We enrolled 72 patients between January 2021 and October 2022 (**Fig. 1**); one participant was enrolled in error, leaving 71 patients included in the intention to treat analyses. Fourteen patients were excluded from the sedative outcomes analysis (eight intervention, six control) due to paralytic administration (4), being transferred out of ICU before study day 3 (2), and a change in sedation goal (e.g., transition to comfort care; 6) and insufficient data (2). Patient demographics are shown in **Table 1**. The participant population was 69% male, mean age 54, with half of participants having one or more comorbidities. The most common cause of admission was for COVID or non-COVID pneumonia. There were baseline differences between the two groups in the proportion with comorbidities (66% of controls vs. 42% of intervention) and the proportion receiving low-dose vasopressors (50% intervention vs. 37% of controls) and the dose of vasopressor used (higher in the intervention group). A higher proportion of the control group was receiving beta-blockers before admission (26% vs. 8%). Almost all participants were receiving propofol as their primary sedative (89%).

The primary sedative doses used are shown in **Figure 2**. Compared with baseline, there was a significantly larger decrease in sedative dose on study day 3 in the propranolol group compared with control (53.9% vs. 33.9% reduction; $p = 0.048$). Secondary outcomes are shown in **Table 2**. The propranolol group had a higher percentage of RASS assessments within the target range (48% vs. 35%; $p < 0.0001$). There were no differences in the proportion of patients who were weaned to the minimum dose of primary sedative indicated in the protocol, and the opioid doses on day 3 were similar in the intervention group compared with controls. There were no significant differences in the proportion of assessments where the patient was delirious, or in ventilator-free days or delirium-free days, or ICU or hospital mortality.

Participants in the intervention group received propranolol for an average of 10 days, at an average daily dose of 90 mg (**Supplementary Table 1**, http://links.lww.com/CCM/H628). Adherence to the propranolol dosing protocol was high overall, with a median of one

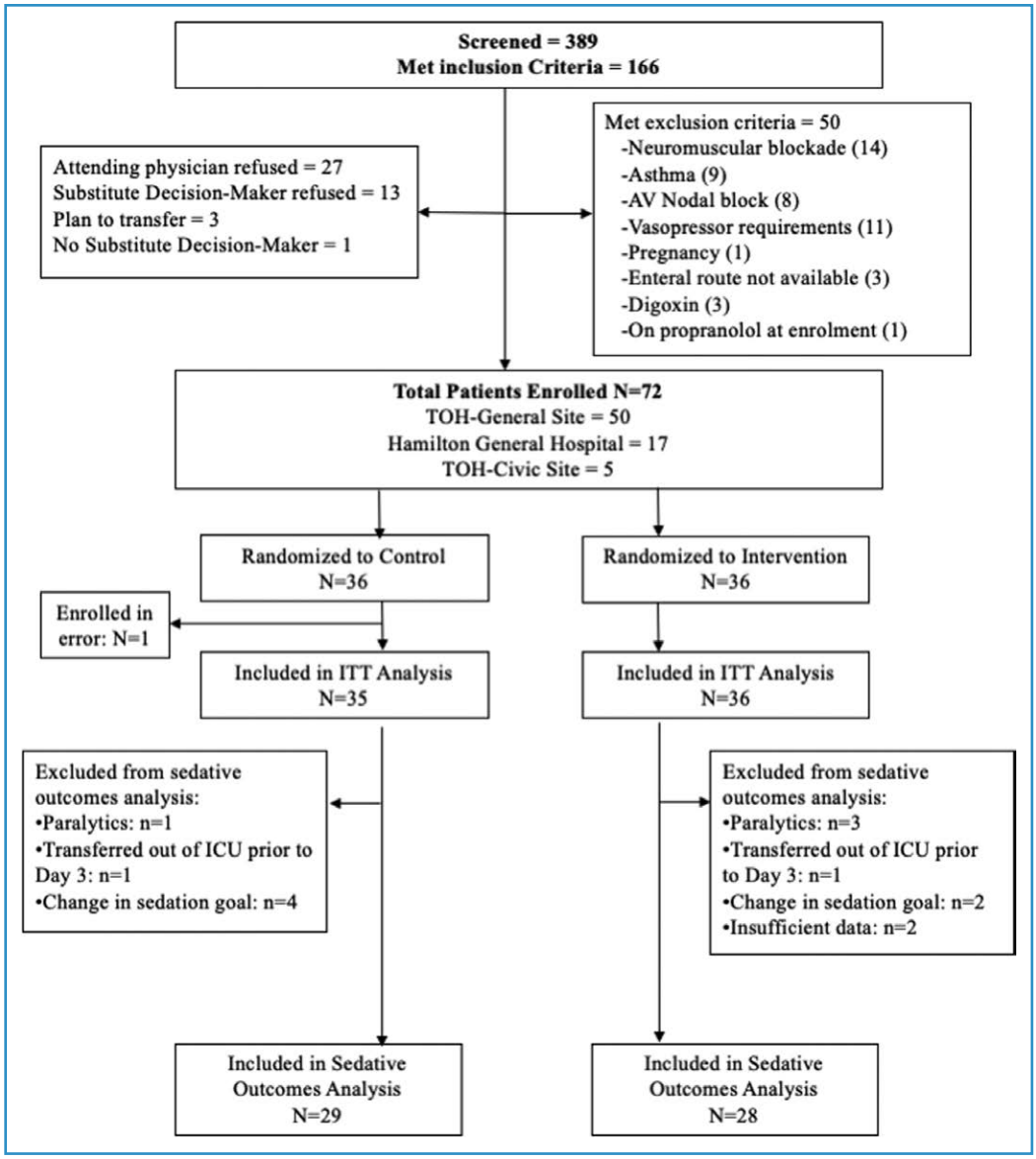

Figure 1. Flow diagram of Propranolol As an Anxiolytic to Reduce the Use of Sedatives for Critically Ill Adults Receiving Mechanical Ventilation (PROACTIVE) patients enrolled and included in analyses. AV = atrioventricular, ITT = intention to treat, TOH = The Ottawa Hospital.

missed dose per participant and four participants who had to interrupt the protocol due to paralytic medications. The overall occurrence rate of adverse events was similar between the two groups (**Supplementary Table 2**, http://links.lww.com/CCM/H628), with slightly more episodes of bradycardia in the control group (3 vs. 1.5; $p = 0.03$).

Table 3 shows the use of other sedative and antipsychotic medications in participants during the study. About half of participants in each group received dexmedetomidine concomitantly with their primary sedative; on day 3, dexmedetomidine use was more common in the control group (11/29, 38%) than in the intervention group (6/28, 21%), but the difference was not statistically significant ($p = 0.17$). Significantly more patients in the control group were prescribed a new parenteral benzodiazepine during the study period (11% vs. 0%; $p = 0.04$). More participants in the intervention group received an antipsychotic during the study period compared with controls (6 vs. 3 patients; $p = 0.3$), although more control participants received a new parenteral benzodiazepine (4 vs. 0 patients; $p = 0.04$). In a post hoc comparison, more patients in the control group underwent an elective tracheostomy (40% vs. 19%) although this difference was not significant ($p = 0.06$).

DISCUSSION

In this multicenter, open-label RCT of patients admitted for mechanical ventilation to a medical-surgical ICU, we found that the addition of propranolol caused a significant reduction in the dose of sedatives used compared with control and better adherence to the sedation target, while adverse events were similar between the two groups. This suggests that propranolol may be a safe and useful sedative-sparing strategy for patients on mechanical ventilation requiring a substantial dose of sedatives and may help preserve sedative supplies in the event of a major surge in demand for mechanical ventilation or during drug shortages, or in low-resource environments.

Studies in traumatic brain injury have shown that propranolol use is associated with reduced agitation (19), shorter length of hospital (16) and ICU stay (16),

TABLE 1.
Participant Demographics and Baseline Clinical Data

Characteristic	Control ($n = 35$)	Intervention ($n = 36$)
Age, mean (SD)	55 (16)	53 (16)
Sex (female), *n* (%)	11 (31)	11 (31)
Medical reason for admission, *n* (%)	25 (71)	28 (78)
Pneumonia (non-COVID)	2 (6)	5 (14)
Pneumonia due to COVID	11 (31)	10 (28)
Nonlung sepsis	4 (11)	1 (3)
Other	8 (23)	12 (33)
Surgical reason for admission (emergency)	8 (23)	7 (19)
Trauma	5 (14)	4 (11)
Surgical reason for admission (elective)	2 (6)	1 (3)
COVID status at enrollment, *n* (%) positive	13 (37)	10 (28)
Richmond Agitation-Sedation Scale target at enrollment, *n* (%)−2 to 0	29 (83)	25 (69)
Confusion Assessment Method for ICU at enrollment, *n* (%)		
Positive	12 (34.29)	6 (16.67)
Negative	4 (11.43)	4 (11.11)
Unable to assess	19 (54.29)	26 (72.22)
Acute Physiology and Chronic Health Evaluation at enrollment, median (IQR)	13 (9–18)	13.5 (9–16.25)
Sequential Organ Failure Assessment at enrollment, median (IQR)	5 (3–6)	4 (2.75–6.25)
Comorbidities, *n* (%)		
Supraventricular arrhythmias, congestive heart failure	0 (0)	0 (0)
Hypertension	19 (54)	12 (33)
Chronic renal failure	4 (11)	2 (6)
Chronic lung disease	1 (3)	3 (8)
Diabetes (type 1 or 2)	12 (34)	5 (14)
Malignancy with treatment in last 3 mo	2 (6)	2 (6)
Documented substance use disorder	9 (26)	7 (19)
Beta-blocker on ICU admission	9 (26)	3 (8)
Eligibility sedative, *n* (%) propofol	31 (89)	32 (89)
Low-dose vasopressor at enrollment, yes, *n* (%)	13 (37)	18 (50)
Dose norepinephrine (24 hr µg total dose) at enrollment, median (IQR)[a]	3,906.73 (3,452.80–5,161.6)	8,592.88 (3,584.80–15,632.91)
Medications at enrollment, *n* (%) receiving scheduled medication		
Propofol infusion	32 (91)	34 (94)
Benzodiazepine	15 (43)	16 (44)
Other sedatives	13 (37)	13 (36)
Antipsychotics	2 (6)	2 (6)
Opioid	29 (83)	32 (89)
Sedative dose (24 hr mg total dose) at baseline, median (IQR)		
Propofol	5,747.50 (4,447.0–6,710.45)	5,320.50 (3,887.00–7,218.50)
Benzodiazepine (midazolam equivalents)	40.00 (11.00–117.50)	48.80 (8.00–240.00)

IQR = interquartile range.
[a]Among those on low-dose vasopressor at enrollment.

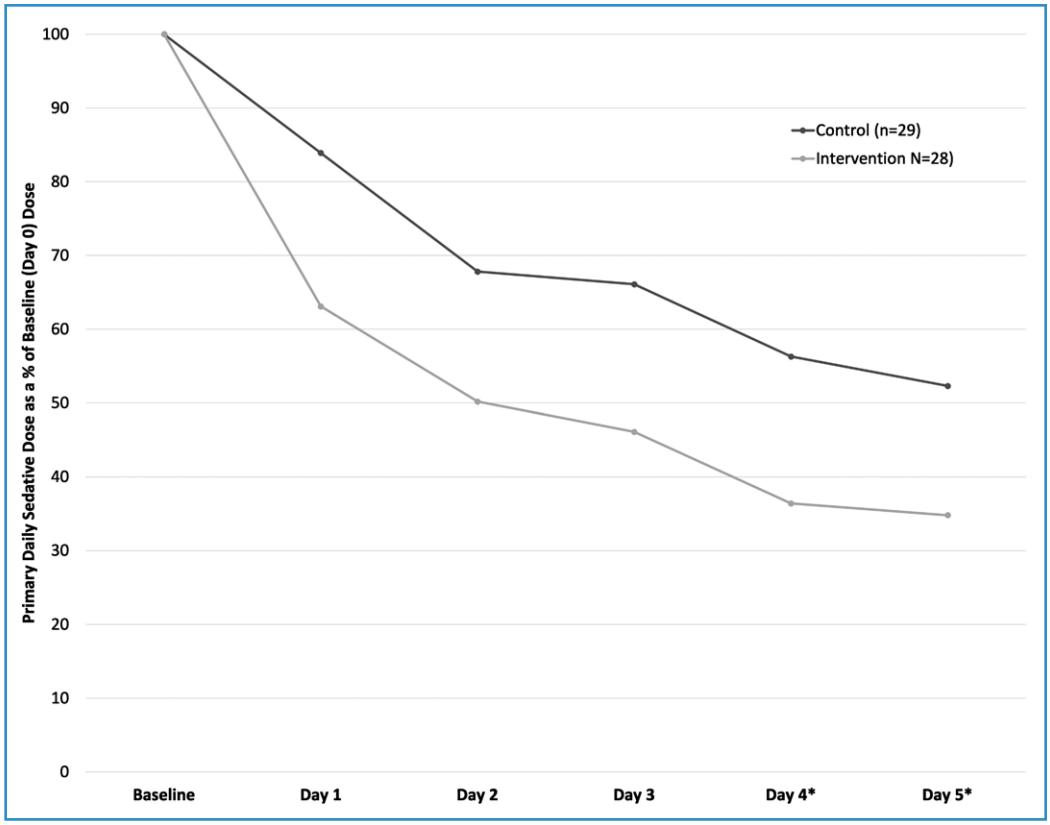

Figure 2. Primary sedative doses during study. *Excludes deceased patients from day 4 ($n = 1$) and day 5 ($n = 2$)—both control patients.

and possibly a lower mortality risk (15, 18), without reports of significant side effects. A meta-analysis of ten RCTs in severely burned patients found propranolol reduced hospital length of stay but not mortality (17). We previously published a single-center retrospective study of 64 mechanically ventilated patients, which found that the initiation of propranolol was associated with an 86% reduction in propofol dose and a 50% reduction in midazolam dose while maintaining the desired sedation (20). The present prospective, randomized study confirms these observational findings in a medical-surgical critical care population.

Some may be hesitant to use beta-blockers in critical illness, but we found that adverse events occurred with the same frequency in our control group, suggesting that enteral propranolol can be used safely in patients receiving mechanical ventilation and low to moderate doses of catecholamines. Morelli et al (22) found that esmolol reduced HR and improved mortality in patients with septic shock requiring high-dose norepinephrine in an open-label RCT.

Dexmedetomidine, an alpha-2 agonist with similar cardiovascular effects to beta-blockers, is an easily titratable first-line sedative that provides rousable sedation and improves critical care outcomes compared with benzodiazepines such as midazolam (1). However, dexmedetomidine use can be limited by cost and the need for deeper sedation. Wang et al (23) performed a systematic review and meta-analysis of the use of clonidine, a lower-cost oral alpha-2 agonist, in the critically ill. They found a small reduction in the dose of opioids administered (standard mean difference, –0.26), a higher occurrence rate of clinically significant hypotension (risk ratio [RR], 3.11), and no difference in ICU mortality, length of stay, or duration of mechanical ventilation. Other sedative-sparing strategies may also be effective, including the use of volatile anesthetics (24, 25), but the need for specialized equipment limits generalizability. Propranolol was first patented in 1962 and is included on the World Health Organization's model list of essential medications (26). Enteral propranolol requires no special equipment, is used for a variety of cardiac, psychiatric, and other conditions, and is commonly available as a generic medication for less than $1 per day at the doses used in this study. Although the purpose of our study was to determine whether propranolol might have a sedative-sparing effect that would help preserve sedative supplies, our findings could also be helpful to ICUs operating on limited budgets, in low- and middle-income countries outside of a pandemic context or during unexpected drug shortages.

Our study was primarily focused on studying the sedative-sparing effects of propranolol, a system-level effect that might be most relevant when sedative supplies are limited. It was not powered to look

TABLE 2.
Secondary Outcomes

Outcome	Control ($n = 35$)	Intervention ($n = 36$)	p
RASS assessments, *n* (%)			**< 0.00001**
Within target	632/1809 (34.94)	825/1728 (47.74)	**< 0.00001**
Below target	721/1809 (39.86)	410/1728 (23.73)	**< 0.00001**
Over target	456/1809 (25.21)	493/1728 (28.53)	**0.03**
RASS within target, *n* (%), yes	632 (34.94)	825 (47.74)	**< 0.00001**
Dose at day 3 < 0.5 mg/kg/hr propofol or < 1.0 mg/hr midazolam, *n* (%), yes[a]	6 (21)	7 (25)	0.76
Change (baseline to day 3) in 24 hr opioid dose (mg parenteral morphine equivalents), mean (SD)[b]	1.24 (47.9)	−12.3 (48.3)	0.38
Ventilator-free days in first 30 d post-randomization, mean (SD)	12.23 (11.54)	13.06 (10.68)	0.77
Ventilator-free days in first 30 d post-randomization, median (IQR)	13 (0–23.50)	15.5 (0–24.00)	0.90
Duration of mechanical ventilation (d), mean (SD)	13.51 (9.88)	11.97 (8.05)	0.66
Duration of mechanical ventilation (d), median (IQR)	13 (5.00–17.50)	11 (5.00–16.00)	0.72
Incident delirium, *n* (%)[c]	16 (45.71)	13 (36.11)	0.47
Proportion of delirium days post-randomization, mean (SD)			
Positive	23.11 (24.83)	28.80 (26.16)	0.35
Negative	27.22 (26.63)	29.35 (28.67)	0.79
Unable to assess	49.66 (29.23)	41.85 (29.52)	0.27
Proportion (%) of delirium days post-randomization, median (IQR)			
Positive	17.65 (0–34.75)	20.71 (3.13–50.00)	0.72
Negative	25.00 (0–43.08)	25.00 (0–46.88)	0.90
Unable to assess	50.00 (22.78–73.86)	33.85 (23.69–55.91)	0.41
Proportion (%) of delirium-negative days post-randomization among days with completed assessment, mean (SD)[d]	50.96 (39.63)	48.94 (37.77)	0.82
Proportion (%) of delirium-negative days post-randomization among days with completed assessment, median (IQR)[d]	50.00 (15.00–95.00)	50.00 (12.50–80.00)	0.91
Mechanical restraints (days used), mean (SD)	4.26 (6.25)	5.61 (7.83)	0.53
Mechanical restraints (days used), median (IQR)	2 (0–5.50)	3 (0–7.25)	0.28
Vasopressor-free days post-randomization, mean (SD)	10.9 (8.68)	12.3 (6.53)	0.84
Vasopressor-free days post-randomization, median (IQR)	7.0 (5–17.50)	9.5 (5–14.25)	0.55
Days from randomization to ICU discharge (excludes deceased), mean (SD)	17.0 (13.8)	17.3 (14.8)	0.80
Days from randomization to ICU discharge (excludes deceased), median (IQR)	11 (6–29.5)	13 (8–20.5)	0.78
ICU length of stay (d), median (IQR)	18 (10–23.5)	18 (11.75–24.75)	0.71
Hospital length of stay (d), median (IQR)[e]	29 (17–58.5)	28 (15–47.25)	0.91
ICU mortality, *n* (%) deceased	8 (23)	9 (25)	1.00
Hospital mortality, *n* (%) deceased	10 (29)	9 (25)	0.79

IQR = interquartile range, RASS = Richmond Agitation-Sedation Scale.

[a]$n = 29$ control; $n = 28$ intervention.

[b]$n = 34$ control; $n = 35$ intervention—one patient excluded from each group due to concomitant receipt of methadone.

[c]Includes patients who went from "unable to assess" to "positive" or "negative" to "positive."

[d]$n = 32$ control; $n = 33$ intervention.

[e]Includes time spent at previous hospital if applicable.

Boldface entries indicate $p < 0.05$.

TABLE 3.
Other Sedatives and Antipsychotic Medications Administered

Medication/Intervention	Control ($n = 35$)	Intervention ($n = 36$)	p
Dexmedetomidine, any study day			
n (%) received medication	19 (54.29)	17 (47.22)	0.55
Days medication received, median (IQR)	4 (3–6)	3 (2–5)	
Dexmedetomidine, day 3			
n (%) received medication	11 (31.43)	6 (16.67)	0.15
Mean total 24 hr dose (SD)	1,129.11 (789.01)	993.66 (901.52)	
Clonidine			
n (%) received medication	3 (8.57)	1 (2.78)	0.29
Days medication received, median (IQR)	4 (3–4)	2 (2)	
Any antipsychotic			
n (%) received medication	3 (8.57)	6 (16.67)	0.31
Days medication received, median (IQR)	4 (3.5–6.5)	8 (6.5–11.75)	
Haloperidol			
n (%) received medication	0 (0)	2 (5.56)	0.16
Days medication received, median (IQR)	0 (0)	2 (2)	
Seroquel			
n (%) received medication	3 (8.57)	4 (11.11)	0.72
Days medication received, median (IQR)	4 (3.5–6.5)	4.5 (2.5–10.5)	
Quetiapine			
n (%) received medication	0 (0)	3 (8.33)	0.08
Days medication received, median (IQR)	0 (0)	8 (4.5–8)	
Loxapine			
n (%) received medication	0 (0)	1 (2.78)	0.32
Days medication received, median (IQR)	0 (0)	11 (11)	
New propofol (among patient not receiving propofol on enrollment)			
n (%) received medication	2 (5.71)	1 (2.78)	0.54
Days medication received, median (IQR)	6.5 (6.25–6.75)	2 (2)	
New benzodiazepine, parenteral			
n (%) received medication	4 (11.43)	0 (0)	**0.04**
Days medication received, median (IQR)	1.5 (1–4.5)	0 (0)	
New benzodiazepine, oral			
n (%) received medication	3 (8.57)	2 (5.56)	0.62
Days medication received, median (IQR)	3 (2.5–3.5)	17.5 (12.25–22.75)	
New tracheostomy during study, *n* (%)	14 (40)	7 (19)	0.06

IQR = interquartile range.
Boldface entry indicates $p < 0.05$.

at patient-centered or patient-level effects such as mortality or other health outcomes, but many of the secondary outcomes showed a nonsignificant trend toward benefit for propranolol. This would need to be assessed in an adequately powered trial. While propofol remains a first-line sedative, a recent updated meta-analysis of propofol compared with any alternative in any setting found a small but significant increased risk of mortality (RR, 1.10) (27). If this small signal applies to critical illness, a reduction in propofol

dose would have at best a modest effect on mortality. Tracheostomy may be associated with reduced duration of mechanical ventilation and ICU stay (28), but if propranolol caused a reduction in the use of tracheostomy, without any impact on duration of ventilation or ICU stay, this might reduce the risk of morbidity from the procedure.

Propranolol has also been used in the management of PTSD, which is a common feature of post-intensive care syndrome (13). Once PTSD is established, propranolol may be effective for blunting the symptoms triggered by traumatic memory reactivation (29). A recent review was inconclusive about the potential for propranolol to prevent the development of PTSD, due to the risk of bias and heterogeneity of results (30). We did not follow our patients beyond discharge to assess for PTSD symptoms, given the limited scope of the study in the pandemic context.

There are important variations in sedation practices around the world, including differing use of medications, protocolized sedation, spontaneous awakening, and spontaneous breathing trials, so the results of a three-site study in Canada may not be generalizable to settings with different sedation practices. For pragmatic reasons, our study was focused on the small minority of mechanically ventilated patients who required high doses of IV sedatives, which also limits generalizability. Our study used an open-label design out of necessity due to the desire for safety and logistical simplicity given the urgency of the research question (Appendix, http://links.lww.com/CCM/H628, for detailed rationale). Because the study was pragmatic, care providers were not restricted in their use of other sedatives, which makes the findings more generalizable. But since the study was also not blinded, we cannot exclude the possibility that they altered their sedation management based on treatment assignment. However, differences in the new prescriptions of parenteral benzodiazepines, and in the use of dexmedetomidine on day 3, would have biased the results toward the null hypothesis, if anything, and we did not detect any substantial difference between the two groups in the use of other sedative or antipsychotic medication. The control group had a higher proportion of sedation assessments outside the RASS target, which could suggest that they were either oversedated compared with the intervention group or that their sedation management was more challenging than the intervention group. We also pragmatically enrolled patients receiving either propofol or midazolam as their primary sedative, rather than focusing on one or the other. It is possible that our signal was driven primarily by effects on propofol (89% of those enrolled) and would not reduce midazolam to a similar degree. We had to exclude ~20% of participants from the analysis of the primary outcome because of early chemical paralysis, death, etc because their sedative goals (and therefore their sedative doses) on day 3 would not have been comparable to the other participants; these were equally split between groups, reducing the possibility of these exclusions biasing the results. We also conducted a large number of secondary analyses on a limited sample size, which increases the possibility of spurious findings in those analyses. Finally, although we did not detect an elevated risk of adverse events in the intervention group, this finding should be interpreted with caution because our study was not powered for this endpoint.

CONCLUSIONS

We found that the use of propranolol as a sedative-sparing strategy resulted in a significant and substantial reduction in the sedative dose required by patients receiving mechanical ventilation. Our findings may be useful in future surges in demand for mechanical ventilation, preserving sedative supplies that were nearly exhausted at multiple points in many countries during the COVID-19 pandemic. They may also be of interest to critical care providers operating on limited budgets or in low- and middle-income countries, where an inexpensive and abundant medication that lowers the need for more expensive sedatives would be welcome. Future studies should confirm our findings in a blinded study and increase the sample size for more patient-centered outcomes, including the impact on mortality and PTSD.

1 *Department of Medicine, University of Ottawa, Ottawa, ON, Canada.*
2 *Bruyere Research Institute, Ottawa, ON, Canada.*
3 *Ottawa Hospital Research Institute, Ottawa, ON, Canada.*
4 *Hamilton Health Sciences, Hamilton, ON, Canada.*
5 *Sinai Health System, Toronto, ON, Canada.*
6 *Department of Medicine, McMaster University, Hamilton, ON, Canada.*

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Dr. Downar, Ms. Lapenskie, and Dr. Fox-Robichaud conceived of the study. Dr. Downar, Ms. Lapenskie, Dr. Kanji, Ms. Watpool, Ms. Haines, Ms. Porteous, Dr. Burry, and Dr. Fox-Robichaud contributed to the design of the protocol. Dr. Downar, Ms. Lapenskie, Dr. Kanji, Ms. Watpool, Ms. Haines, Ms. Saeed, Ms. Porteous, Dr. Burry, Ms. Himed, Mr. Anderson, and Dr. Fox-Robichaud participated in data collection. All authors contributed to analysis and interpretation of the data, and the drafting or revision of the article. All authors approved the final version submitted for publication.

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For information regarding this article, E-mail: jdownar@toh.ca

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