J Crit Care 79 (2024) 154433

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Research letter: Clonidine is associated with faster first resolution of incident ICU delirium than antipsychotics

ARTICLE INFO

Keywords
Clonidine
Haloperidol
Quetiapine
Delirium
Intensive care

Clonidine and antipsychotics are often used to treat delirium in the intensive care unit (ICU) despite a lack of evidence supporting their benefit and guidelines not recommending routine use [1]. While one randomized trial found clonidine reduced postoperative delirium severity after cardiovascular surgery, it was small and evaluated a population with low severity of illness [2]. A recent cohort study [3] found less next-day delirium resolution with exposure to clonidine, haloperidol or both, but it failed to evaluate the time to first delirium resolution after drug initiation, exclude patients receiving clonidine/haloperidol prior to delirium, or consider quetiapine use [4]. Moreover, it defined delirium resolution to be ≥2 days free of delirium, a duration too long to detect a first resolution of delirium of 24 h that may be clinically significant. A pharmacologic intervention, when combined with non-pharmacologic reduction strategies, that reduces delirium faster may improve ICU and post-ICU outcomes [1]. We sought to compare the time to first incident delirium resolution in critically ill adults managed with either clonidine or antipsychotics.

We conducted an IRB-approved prospective cohort study of consecutive adults admitted to one mixed ICU between 2011 and 2019 who were administered clonidine or an antipsychotic (haloperidol, quetiapine, or both) within 24 h of incident delirium occurrence. For the purposes of our analysis, incident delirium was defined as a day with ≥1 positive Confusion Assessment Method-ICU (CAM-ICU), confirmed using a validated protocol, that first occurred after ICU admission. We excluded patients who were admitted with acute substance withdrawal, received both clonidine and an antipsychotic, received either before delirium occurrence, or experienced coma (Richmond Agitation Scale Score = −4/−5) after delirium occurrence. The first ICU day without a positive CAM-ICU assessment after drug initiation indicated delirium resolution. A Cox proportional hazards regression model that accounted for baseline [age, medical (vs. surgical) admission, APACHE-IV score, Charlson Comorbidity Index] and daily (SOFA, invasive mechanical ventilation use and opioid, benzodiazepine, and propofol exposure) variables, and daily clonidine or antipsychotic use, was constructed. Missing model variables were addressed using simple imputation with the median.

Delirium occurred in 1430/4075 (35.1%) of the patients. Among the

Table 1
Demographics and characteristics of delirium patients by clonidine or antipsychotic exposure.

Characteristic	Clonidine only (*n* = 77)	Antipsychotic only (*n* = 149)	*P* value
Clonidine and antipsychotic use			
Time from incident delirium to first initiation of clonidine or an antipsychotic, median (IQR)	0 (0,1)	0 (0, 1)	0.33
Presence of agitation on the day of clonidine or antipsychotic initiation, n (%)	15 (19.5%)	18 (12.1%)	0.20
Duration of clonidine or antipsychotic treatment, median (IQR)[A]	2 (1,2)	2 (1,3)	0.42
Baseline variables with the potential to influence delirium duration			
Age, median (IQR)	61 (51, 70)	66 (58, 76)	<0.01
Medical, n (%)	40 (51.9%)	51 (34.2%)	0.02
APACHE IV score, median (IQR)	71.5 (51.3, 90.0)	72.0 (54.0, 82.5)	0.65
Charlson Comorbidity Score, median (IQR)	1 (0,2)	1 (0, 2)	0.08
ICU variables with the potential to influence delirium duration[B]			
Highest daily RASS score, median (IQR)	1 (1,1)	1 (1, 1)	0.96
Lowest daily RASS score, median (IQR)	−2 (−4, −1)	-2 (−3,−1)	0.22
Agitation (RASS ≥2) ever, n (%)	15 (19.5%)	31 (20.8%)	0.95
Mechanical ventilation use ever, n (%)	75 (97.4%)	125 (83.9%)	<0.01
Highest SOFA score, median (IQR)	7 (5, 8)	7 (6, 10)	0.06
Benzodiazepine use ever, n (%)	24 (31.2%)	69 (46.3%)	0.04
Propofol use ever, n (%)	42 (54.5%)	27 (18.1%)	<0.01
Opioid use ever, n (%)	28 (36.4%)	5 (3.4%)	<0.01
Outcome			
Delirium resolution in the ICU, n (%)	54 (70.1%)	91 (61.1%)	0.23
Time to first ICU delirium resolution from the day clonidine or an antipsychotic was administered, median (IQR), days	2 (2,3)	2 (2, 3)	0.06

[A] Until delirium resolution or ICU discharge (whichever came first).
[B] On and after the ICU day clonidine or an antipsychotic was initiated.

https://doi.org/10.1016/j.jcrc.2023.154433

Available online 26 September 2023

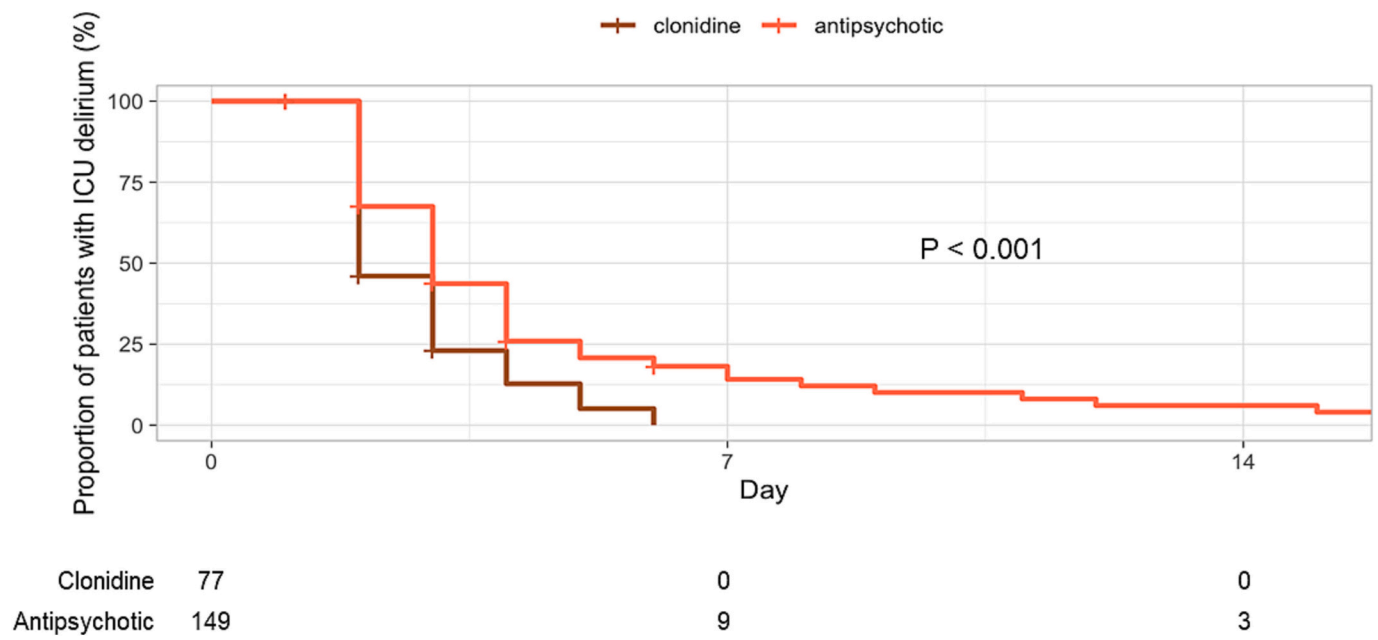

Fig. 1. Comparison of the time to first resolution of ICU incident delirium between the clonidine and antipsychotic groups.

1074 patients with delirium who also received clonidine or an antipsychotic, 884 were excluded (340 with delirium at ICU admission, 88 receiving clonidine or an antipsychotic at ICU admission, 227 receiving clonidine or an antipsychotic prior to delirium, 150 receiving both, and 35 with post-delirium coma) leaving 77 clonidine patients and 149 antipsychotic patients in the analysis. At ICU baseline, the clonidine (vs. antipsychotic) group was younger and more likely medical, mechanically ventilated, and to receive propofol and opioids; severity of illness and ICU agitation occurrence was similar (Table 1). Total median (IQR) duration of therapy (until delirium resolution or ICU discharge) was similar [clonidine, 2(1,2) vs. 2(1,3) days, $P = 0.42$]. While delirium resolved in a similar proportion of clonidine (vs. antipsychotic) patients [54/77 (70%) vs 91/149 (61%), $P = 0.23$] over the ICU stay, clonidine (vs. antipsychotic) use was associated with a faster time to first delirium resolution ($P < 0.001$)(Fig. 1). Clonidine (vs. antipsychotic) use was associated with a greater daily probability of ICU delirium resolution (adjusted Hazard Ratio = 1.83, 95% CI 1.23, 2.70).

After adjusting for both baseline and time-varying covariates, we found treatment of ICU incident delirium with clonidine, rather than haloperidol or quetiapine, was associated with an 83% increased rate of ICU delirium resolution. This is a clinically important finding given a shorter duration of ICU delirium is associated with reduced mortality and long-term cognitive impairment [1]. Another alpha−2 agonist, dexmedetomidine, compared to other sedatives, has been shown to significantly reduce delirium in the ICU [5]. Our analysis should be considered exploratory and hypothesis-generating given its potential limitations, including data derivation from only one hospital, the lack of consideration of delirium symptoms and the potential for residual confounding. Although delirium reoccurrence in the 24 to 48 h period after it first resolved was similar between the clonidine and antipsychotic groups (20.0% vs 21.3%, $P = 0.92$), the fact it occurred in one-fifth of patients suggests additional research regarding the appropriate duration of therapy is important. We were not able to account for the daily presence of hyperactive versus hypoactive delirium in our model given patients had mixed delirium (both hyperactive and hypoactive) on most ICU days. Our results highlight the importance of conducting further randomized controlled trials of clonidine as a treatment for delirium in critically ill adults.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None declared.

Acknowledgements

Study concept and design: all authors. Data acquisition: AJCS. Data analysis and interpretation: all authors. All authors drafted or revised the manuscript for important intellectual content, ensure the accuracy and integrity of the manuscript and approved the version to be published.

References

[1] Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit. Crit Care Med 2018;46(9): e825–73.
[2] Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. Interact Cardiovasc Thorac Surg 2010;10 (1):58–62.
[3] Devlin JW, Roberts R, Fong JJ, et al. Efficacy and safety of quetiapine for delirium in the ICU: a randomized, double-blind, placebo- controlled pilot study. Crit Care Med 2010;38(2):419–27.
[4] Smit L, Dijkstra-Kersten SMA, Zaal I, et al. Haloperidol, clonidine, and resolution of delirium in critically ill patients: a prospective cohort study. Intensive Care Med 2021;47(3):316–24.
[5] Lewis K, Alshamsi F, Carayannopoulos KL, et al. Dexmedetomidine vs other sedation strategies in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. Intensive Care Med 2022;48(7):811–40.

Ting Ting Wu[a,b], Gillian Steiger[c], Louisa Smith[a,d], John W. Devlin[b,c,*], Arjen J.C. Slooter[e,f]
[a] *Department of Health Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA, USA*
[b] *Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA*

[c] *School of Pharmacy and Pharmaceutical Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA, USA*
[d] *The Roux Institute, Northeastern University, Portland, ME, USA*
[e] *Departments of Psychiatry and Intensive Care Medicine, University Medical Center (UMC) Utrecht Brain Center, Utrecht University, Utrecht, the Netherlands*
[f] *Department of Neurology, UZ Brussel and Vrije Universiteit Brussel, Brussels, Belgium*

[*] Corresponding author at: School of Pharmacy and Pharmaceutical Sciences, Northeastern University, 360 Huntington Ave, RD 216F, Boston, MA 02115, USA.
E-mail address: j.devlin@northeastern.edu (J.W. Devlin).