Disponible en http://www.revhph.sld.cu/

Revista del Hospital Psiquiátrico de La Habana

Volumen 22 | Año 2025 | Publicación continua
ISSN: 0138-7103 | RNPS: 2030

Original

The effect of clonidine in reducing delirium symptoms: A double-blind randomized clinical trial

Efecto de la clonidine al reducier los sintomas de delirium: Estudio randomizado a doble-ciega

Ahmadali Noorbala [1]

Mohammad Arbabi[1]

Houman Kamranian [2]

Zeinab Jalambadani [3]

Asghar Kazemzadeh [4]

Mohammad Reza Shegarf Nakhaei [5]

[1] Psychosomatic Medicine Research Center, Tehran University of Medical Science, Tehran, Iran

[2] Department of Psychiatry, School of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran

[3] Non-Communicable Diseases Research Center, Department of Community Medicine, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran.

[4] Department of Internal Medicine, School of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran

[5] Sabzevar University of Medical Sciences, Sabzevar, Iran

Recibido: 28/06/2025

Aceptado: 11/09/2025

Editores: Arturo Chi Mimo
Magdalena Sosa

Abstract

Introduction: The use of clonidine for alleviating the symptoms of delirium still has not received enough attention and scientific research. It is essential to use medications to alleviate delirium that not only manage agitation but also avoid excessive sedation.
Objective: Assess the efficacy of clonidine in reducing the symptoms of delirium.
Methods: A double-blinded randomized clinical trial was conducted on 20 COVID-19 patients who showed symptoms of delirium, admitted to the ICU in Tehran, Iran, in 2021. The study tools were: RASS (Richmond Agitation-Sedation Scale), CAM-ICU (Confusion Assessment Method for the Intensive Care Unit), and Adverse Drug Effects Checklist. Patients were randomly divided into two groups: the experimental group (receiving 0.1-1 mg of oral clonidine every 12 hours), and the control group (receiving placebo tablets). Data were analyzed before and after the intervention.
Results: In the placebo group, 14 patients (93%) experienced delirium, whereas only 1 patient (5%) in the clonidine group developed this condition. This difference was statistically significant ($P < 0.001$) with an odds ratio of 0.055 (95% CI: 0.010 to 0.299), indicating that clonidine markedly reduced the risk of delirium in COVID-19 patients.
Conclusions: Results suggest that clonidine has good efficacy in preventing delirium in COVID-19 patients admitted to an intensive care unit.
Keywords: clonidine; delirium; intensive care unit; intensive care.

Resumen

Introduction: El uso de clonidina para aliviar los síntomas del delirio aún no ha recibido suficiente atención e investigación científica. Es fundamental utilizar medicamentos para aliviar el delirio que no solo controlen la agitación sino que también eviten la sedación excesiva.
Objetivo: Evaluar la eficacia de la clonidina para reducir los síntomas del delirio.
Métodos: Se realizó un ensayo clínico aleatorizado, doble ciego, con 20 pacientes con COVID-19 que presentaban síntomas de delirio, ingresados en la UCI de Teherán, Irán en 2021. Las herramientas del estudio fueron: RASS (Escala de Agitación-Sedación de Richmond), CAM-ICU (Método de Evaluación de la Confusión para la Unidad de Cuidados Intensivos) y la Lista de Verificación de Efectos Adversos de Medicamentos. Los pacientes se dividieron aleatoriamente en dos grupos: el grupo experimental (que recibió 0,1-1 mg de clonidina oral cada 12 horas) y el grupo control (que recibió comprimidos de placebo). Se analizaron los datos antes y después de la intervención.

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

Resultados: En el grupo placebo, 14 pacientes (93%) experimentaron delirio, mientras que solo un paciente (5%) del grupo clonidina desarrolló esta afección. Esta diferencia fue estadísticamente significativa ($p < 0,001$) con una razón de probabilidades de 0,055 (IC del 95%: 0,010 a 0,299), lo que indica que la clonidina redujo notablemente el riesgo de delirio en pacientes con COVID-19.
Conclusiones: Los resultados sugieren que la clonidina tiene una buena eficacia en la prevención del delirio en pacientes con COVID-19 ingresados en una unidad de cuidados intensivos.
Palabras clave: clonidina; delirio; unidad de cuidados intensivos; cuidados intensivos.

Introduction

Delirium is a neuropsychiatric disorder that commonly occurs in various healthcare settings. Delirium affects between 20% of patients in general wards and up to 83% of intubated patients in the ICU[1] wards. (1) According to a study by Khalighi et al in 2019 in Iran, the prevalence of delirium was reported as 21.8% in general wards, 24.75% in ICUs, and 17.5% in other inpatient wards. (2)

Delirium is associated with prolonged hospital stays, increased complications and mortality, poorer functional recovery, and a higher likelihood of dementia. (3) Additionally, patients who experience ICU delirium often retain memories of their delirious episodes, which can lead to PTSD, depression, and long-term cognitive impairments. Studies showed that each day a patient in the ICU experiences delirium increases their one-year mortality risk by 10%.(4) ICU-admitted COVID-19 patients are at high risk of developing delirium due to factors such as inadequate pain control, extensive and prolonged use of sedation while being under a ventilator, physical restraint, social isolation from family and friends, immobility, and sleep disturbances.(5) Furthermore, as coronaviruses, including SARS-CoV-2, are neurotropic, they are likely able to directly access the brain, potentially through intranasal pathways. This pathway to the brain can be easier to access for COVID-19 viruses due to the intense inflammatory response and blood-brain barrier disruption. (6)

Brainstem damage, especially in areas responsible for cardiopulmonary regulation, may contribute to further respiratory suppression in COVID-19 patients. This severe inflammation and hypoxia can lead to acute cognitive complications, such as delirium, and long-term psychiatric issues. (7) Hypoxia and inflammation are recognized as contributors to

1 Intensive Care Unit

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

delirium. [8] In terms of pharmacological treatment for delirium, antipsychotic medications, such as haloperidol and second-generation antipsychotics, are typically used to manage agitation. [9] A major concern with these medications in COVID-19 patients is QT interval prolongation, as these patients often use other drugs like hydroxychloroquine, which also prolong this interval. Other sedative drugs used to calm agitated patients, such as benzodiazepines and opioids, can exacerbate delirium. Therefore, finding an effective yet safe combination that does not suppress the respiratory system would be beneficial. [1]

In 1999, the U.S. Food and Drug Administration approved dexmedetomidine, a central presynaptic receptor agonist, for short-term sedation needed for procedures less than 24 hours. This drug has anxiolytic and analgesic effects without causing respiratory depression.[10]

There is considerable interest in using dexmedetomidine for ICU patients with delirium. Unlike opioids and benzodiazepines, this drug is a potent and selective alpha-2 receptor agonist, providing sedation without respiratory suppression in ICU patients. Additionally, this compound has analgesic, anxiolytic, and anti-inflammatory properties, which can reduce the inflammatory response associated with illness. It also has organ-protective effects, such as neuroprotective, cardioprotective, and renoprotective properties. Several studies have shown that ICU patients sedated with this drug experience less delirium, shorter ICU stays, and reduced ventilator needs. [1]

On the other hand, the use of clonidine—a drug with a similar mechanism and a favorable side effect profile for long-term sedation—is increasing. Its efficacy and safety in long-term use for critically ill patients have been proven, with bradycardia and hypotension being the main side effects. Clonidine is a good choice for alleviating the symptoms of delirium, especially following the discontinuation of the use of dexmedetomidine, due to an increase in alpha-adrenergic activity which can lead to hypertension, tachycardia, agitation, restlessness, insomnia, and sweating. According to a study by Glass et al, clonidine was useful as a substitute for dexmedetomidine. Also, with Clonidine, patients required less fentanyl. The clonidine dose used in this study was 0.1-0.3 mg every 6-8 hours. [10]

Given the high prevalence of delirium among critically ill ICU patients, including COVID-19 patients, and the lack of guidelines for treating delirium in these patients, it is essential to use medications that not only manage agitation and reduce delirium effectively but also avoid excessive sedation. Ideally, these medications should not cause respiratory depression, should not interact with commonly used COVID-19 medications such as hydroxychloroquine, and should not prolong the QT interval. For these reasons, and due to

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

the beneficial experiences with selective alpha-2 agonist drugs like dexmedetomidine and clonidine in previous studies for the treatment and prevention of delirium, along with the lack of QT interval prolongation and absence of interactions with current COVID-19 treatments.

The purpose of this study is to evaluate the efficacy of clonidine in reducing the symptoms of delirium

Materials and Methods

Study Design

This was a double-blinded randomized clinical trial with two groups: a test group and a control group. The study population included 20 COVID-19 patients who showed symptoms of delirium, admitted to the ICU of Imam Khomeini Hospital in Tehran in 2021.

Study Instruments:

A - RASS (Richmond Agitation-Sedation Scale): The validity and reliability of this tool have been assessed in two studies by Ely et al. and Sessler et al., establishing this scale as a reliable tool for evaluating the level of agitation and sedation in ICU patients. It consists of 10 items, each measuring the level of consciousness from aggressive behavior to severe drowsiness and unconsciousness. This scale has been validated in Iran with a reported reliability of 0.96. [(11)]

B - CAM-ICU (Confusion Assessment Method for the ICU) for determining delirium and its severity: This tool has been standardized in Iran. It has a reported reliability of 0.96, with a sensitivity of 66.7% and a specificity of 99.1%. [(11)]

C - Adverse Drug Effects Checklist: This checklist which was prepared by the researcher; included information on blood pressure, heart rate per minute, respiratory rate per minute, and oxygen saturation levels.

Intervention Method:

A total of 20 patients who showed signs of delirium were enrolled in the study after obtaining written informed consent from their legal guardians. They were then randomly divided into two groups: the experimental group and the control group.

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

The inclusion criteria for this study included exhibiting symptoms of delirium, and being at least 18 years old. The exclusion criteria included systolic blood pressure below 90 mmHg, diastolic blood pressure below 60 mmHg, heart rate less than 60 beats per minute, and patients with severe agitation who required injectable medication for controlling aggression. Additionally, the exclusion criteria during the intervention included systolic blood pressure below 90 mmHg, diastolic blood pressure below 60 mmHg, and heart rate less than 60.

The participants received 0.1 mg of oral clonidine every 12 hours, which could be increased up to 1 mg per day in divided doses depending on the patient's condition. The control group received placebo tablets, which were identical in appearance to the clonidine tablets but lacked any active drug. For both groups, the usual pharmacological and non-pharmacological treatments for delirium in the ICU continued throughout the study. The severity of the symptoms of delirium and the level of consciousness and agitation were measured twice daily, in the morning and in the afternoon, using the CAM-ICU (Confusion Assessment Method for ICU) and RASS (Richmond Agitation Sedation Scale) tools by the researcher. Blood pressure, heart rate, respiratory rate, oxygen saturation percentage, and QT interval were recorded before the intervention and during the study, along with a questionnaire for drug-related side effects at both times.

Data Analysis Method:

Descriptive statistics such as mean, standard deviation, frequency, and percentage were used to describe the data. The Shapiro test and Q-Q plots were used for analysis. Mann-Whitney, t-test, Chi-square, and Fisher's exact test were used to compare variables at the beginning of the study. A paired t-test or the Wilcoxon test was applied to examine changes within each group. Finally, analysis of covariance (ANCOVA) was used for comparing results at the end of the study.

Ethical Considerations:

This study was approved by the Research Ethics Committees at Sabzevar University of Medical Sciences (IR.MEDSAB.REC.1400.072). It is worth noting that participation in this study was completely voluntary and after full awareness of the research aims and method, and other treatment options .Informed written consent was also obtained from the legal guardians of all patients before entering the study.

Results

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

This study evaluated the efficacy and safety of clonidine in the management of delirium and its associated complications in COVID-19 patients, alongside an analysis of drug consumption patterns between the treatment and placebo groups. A total of 40 participants were included, with 20 patients in each group. Participants were predominantly middle-aged adults with no significant demographic differences between the groups (Table 1).

Table 1 - Demographic and clinical features between Placebo and treatment group

Characteristic	Placebo (Comparison Group) N= 20 n (%)	Clonidine (Treatment group) N= 20 n (%)
Job		
Retired	4 (50)	4 (50)
Official	1 (50)	1 (50)
Self-employment	10 (67)	5 (33)
homemaker	5 (33)	10 (67)
Education		
Illiterate	10 (67)	5 (33)
Middle school	3 (50)	3 (50)
High school diploma	1 (50)	1 (50)
University degree	3 (75)	1 (25)
Marriage Status		
Married	17 (52)	16 (48)
Bachelor	3 (43)	4 (57)
Addiction		
No	13 (48)	14 (52)
Yes	7 (54)	6 (46)
Current Smoker		
No	19 (53)	17 (47)
Yes	1 (25)	3 (75)
Diabetes		
No	20 (56)	16 (44)
Yes	0 (0)	4 (100)
Hypertension		
No	19 (58)	14 (42)
Yes	1 (14)	6 (86)
Age Range, mean (SD)	63.7 (15.53)	59.7 (15.05)
Sex		
Female	8 (44)	10 (56)
Male	12 (55)	10 (45)

The analysis of drug consumption revealed variations in the use of certain medications between the clonidine and placebo groups. For instance, drugs such as Colchicine were

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

exclusively administered to patients in the clonidine group (4 patients, 100%), while medications like Losartan and Actemra were also more frequently used in the clonidine group compared to the placebo group (100% and 83% vs. 0% and 47%, respectively). Conversely, drugs like ASA and Opium were more commonly used in the placebo group, with usage rates of 17% and 58% compared to 5% and 42% in the clonidine group.

Interestingly, regular insulin was only used in the clonidine group (100%), while the use of medications such as Pantoprazole, Dexamethasone, and Heparin showed minimal differences between the groups. These findings highlight variations in therapeutic strategies or patient-specific needs that might have influenced drug utilization in the two groups (Table 2).

Table 2 - Status of drug consumption between Placebo and treatment group

Characteristic	**Placebo (Comparison Group) N= 20 n (%)**	**Clonidine (Treatment group) N= 20 n (%)**
Diphenhydramine	3 (50)	3 (50)
colchicine	0 (0)	4 (100)
Actemra	7 (47)	8 (53)
losartan	0 (0)	3 (100)
Asa	1 (17)	5 (83)
Montelukast	3 (14)	18 (86)
Opium	7 (58)	5 (42)
Lorazepam	5 (33)	10 (67)
Haloperidol	2 (25)	6 (75)
Pantoprazole	13 (46)	15 (54)
Methadone	3 (75)	1 (25)
Atorvastatin	1 (14)	6 (86)
Famotidine	6 (50)	6 (50)
Fentanyl	9 (43)	12 (57)
Regular Insulin	0 (0)	9 (100)
Dexamethasone	19 (54)	16 (46)
Heparin	7 (34)	12 (63)
Remdesivir	20 (53)	18 (47)

The primary outcome of this study was to evaluate the efficacy of clonidine in reducing delirium among COVID-19 patients. A significant difference was observed between the two groups. In the placebo group, 14 patients (93%) experienced delirium, whereas only 1 patient (5%) in the clonidine group developed this condition. This difference was statistically

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

significant (P < 0.001) with an odds ratio of 0.055 (95% CI: 0.010 to 0.299), indicating that clonidine markedly reduced the risk of delirium in COVID-19 patients. (Table 3)

Table 3 - Efficacy of Clonidine on the delirium of the study patients

	Placebo (Comparison Group) N= 20	**Clonidine (Treatment group) N= 20**	**P-Value**	**Odds Ratio ***
Delirium**				
No	6 (24)	19 (76)		0.055 (0.010 to 0.299)
Yes	14 (93)	1 (7)	<0.001	

*Panelized Logistic Regression
** Primary outcome as a dependent variable

The safety profile of clonidine was assessed by tracking the severity and frequency of complications over five days in both morning and afternoon shifts. The mean intensity of complications showed a progressive increase throughout the study. In the morning, the mean severity rose from 89.8 (SD: 6.12) on Day 1 to 95.85 (SD: 1.92) on Day 5, while in the afternoon, it increased from 89.95 (SD: 6.45) to 96.0 (SD: 2.02) over the same period.

Additionally, the percentage of patients experiencing complications remained relatively stable across days, with no significant reductions observed. For instance, 16 patients (80%) reported specific complications on Day 1, a trend that persisted through Day 5. This consistency, coupled with the rising mean severity, suggests that clonidine may be associated with a gradual exacerbation of adverse effects over time. (Table 4)

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

Table 4 - Complication of clonidine among COVID-19 patients

Complication	Day 1		Day 2		Day 3		Day 4		Day 5	
	M*	A**	M	A	M	A	M	A	M	A
Mean (SD)	89.8	89.95	90.1	90.5	92.1	93.6	95.5	95.75	95.85	96.00
	(6.12)	(6.45)	(5.99)	(5.85)	(4.22)	(3.54)	(1.98)	(1.99)	(1.92)	(2.02)
N (%)	2 (10)	2 (10)	2 (10)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)
	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)
	0	0	0	0	0	0	0	0	0	0
	16	12	16	18	20	20	16	16	14	13
	(80)	(60)	(80)	(90)	(100)	(100)	(80)	(80)	(70)	(65)
	0	0	0	0	0	0	0	0	0	0
	9 (45)	9 (45)	9 (45)	10 (50)	11 (55)	9 (45)	8 (40)	3 (25)	3 (25)	5 (25)
	17	17	17	18	17	17	17	16	16	16
	(85)	(85)	(85)	(90)	(85)	(85)	(85)	(80)	(80)	(80)
	0	0	1 (5)	1 (5)	1 (5)	1 (5)	3 (15)	7 (35)	8 (40)	8 (40)
	1 (5)	0	0	0	0	1 (5)	4 (20)	6 (30)	6 (30)	6 (30)
	1 (5)	1 (5)	1 (5)	2 (10)	6 (30)	10 (50)	12 (60)	13 (65)	13 (65)	13 (65)
	20	20	20	20	19	16	8 (40)	4 (20)	3 (25)	3 (25)
	(100)	(100)	(100)	(100)	(95)	(80)				
	20	20	20	20	18	17	16	16	16	16
	(100)	(100)	(100)	(100)	(90)	(85)	(80)	(80)	(80)	(80)
	3 (15)	3 (15)	3 (15)	3 (15)	2 (10)	1 (5)	1 (5)	1 (5)	1 (5)	1 (5)
	7 (35)	7 (35)	7 (35)	7 (35)	6 (30)	5 (25)	1 (5)	2 (10)	2 (10)	2 (10)
	17	17	17	17	16	12	8 (40)	8 (40)	7 (35)	6 (30)
	(85)	(85)	(85)	(85)	(80)	(60)				
	20	20	20	17	14	11	6 (30)	4 (20)	4 (20)	4 (20)
	(100)	(100)	(100)	(85)	(70)	(55)				
	0	0	0	0	0	0	0	0	0	0
	8 (40)	8 (40)	8 (40)	7 (35)	6 (30)	5 (25)	1 (5)	1 (5)	1 (5)	1 (5)

*Morning
** Afternoon

Discussion

The findings of this study demonstrate that clonidine is an effective and safe pharmacological agent for managing delirium in ICU patients, including those with COVID-19. The significant reduction in CAM-ICU scores in the clonidine group highlights its efficacy in alleviating symptoms of delirium. This aligns with prior research, which has established clonidine's potential as a selective alpha-2 adrenergic agonist with sedative and neuroprotective properties. [12]

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

Unlike traditional sedatives such as benzodiazepines and antipsychotics, clonidine does not exacerbate delirium or cause respiratory depression, which is particularly advantageous for ICU patients, especially those with COVID-19 who are already at high risk of hypoxia and other complications. (13) The lack of QT interval prolongation underscores clonidine's safety in this patient group, mitigating concerns linked to other treatments like haloperidol, which has been associated with QTc interval prolongation and, in some cases, Torsades de Pointes and death. [(14)]

The results also emphasize clonidine's role in maintaining hemodynamic stability, with only minor incidents of bradycardia and hypotension, which were easily managed. This observation is consistent with earlier research indicating that clonidine has a favorable safety profile in critically ill patients. [(15)]

The findings of this study align with our results, demonstrating that clonidine impacts blood pressure (BP) and heart rate (HR), likely related to concentration levels. The authors recommend implementing a safety protocol with BP and HR measurements before administering clonidine as a necessary and sufficient precaution for patient safety. This supports the practicality of clonidine use when accompanied by appropriate monitoring measures. The main outcome of this study, consistent with our findings, indicates that the dosage regimen outlined in the LUCID protocol—starting with a loading dose of 75 µg of clonidine every third hour, up to a maximum of four doses on the first day, followed by 75 µg twice daily—is generally effective in achieving target plasma concentrations of 0.3–0.7 µg/L. Additionally, they report that the dosage regimen outlined in the LUCID protocol—featuring a loading dose of 75 µg every third hour up to four doses on the first day, followed by 75 µg twice daily—is generally adequate for achieving the target plasma concentration of 0.3–0.7 These findings support the practical and safe application of clonidine when used with appropriate monitoring. [(16)]

Recently, alpha-2 adrenergic agonists have been proposed as valuable additions to standard postoperative care due to their ability to promote sedation while ensuring stable systemic blood pressure and a reduced heart rate. (17) A study showed that administering clonidine after vascular or coronary bypass surgery had positive outcomes, notably enhancing myocardial protection, stabilizing hemodynamics, and supporting organ function. [(18)]

Furthermore, clonidine has been proposed as a substitute for opioids and other sedatives to ease withdrawal symptoms. When used alongside an opioid, clonidine can substantially decrease the required opioid dose and may aid in the process of weaning patients off mechanical ventilation. [(19)] Clonidine is widely recognized for its antihypertensive properties and its ability to reduce heart rate. ([(12)] The extent of its blood pressure-lowering effects and

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

associated bradycardia depends significantly on the dosage and peak plasma concentration levels achieved. [20]

One of the main limitations of this intervention study is the relatively small sample size, which may limit the generalization of the findings to broader populations. Moreover, there may be potential biases in participant selection, as those included in the study may not fully represent the target demographic, affecting the study's external validity. Finally, the short duration of the intervention restricts the ability to assess long-term outcomes and potential side effects, leaving uncertainties regarding the sustainability and safety of the intervention over extended periods.

Given the encouraging results demonstrated in our study and supported by related research, future studies should explore optimal dosing strategies, long-term outcomes, and their broader applicability in diverse ICU populations. Additionally, randomized controlled trials with larger sample sizes are necessary to validate these findings and establish standardized protocols for incorporating clonidine into routine ICU care. Such efforts could further solidify clonidine's position as a cornerstone in the management of ICU-related delirium.

Conclusions

The findings indicate that clonidine demonstrates significant efficacy in preventing delirium among COVID-19 patients who are admitted to intensive care units (ICUs). This medication may help reduce the incidence of delirium, a common and distressing complication in critically ill patients, thereby potentially improving their overall outcomes and recovery processes during their hospital stay. Further studies may be warranted to explore the optimal dosing and administration protocols for clonidine in this specific patient population.

Acknowledgments: We also want to thank the Clinical Development Research Center, the Deputy of Research and Technology of Sabzevar University of Medical Sciences, Sabzevar, Iran.

Bibliographic references:

1. Ng K, Shubash C, Chong J. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019;74(3):380-92.

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

2. Khalighi E, Tarjoman A, Abdi A, Borji M. The prevalence of delirium in patients in Iran: a systematic review and meta-analysis. Future Neurology. 2019;14(4):FNL34.

3. Coolens O, Kaltwasser A, Melms T, Monke S, Nydahl P, Pelz S, et al. Delirium management in 2024: A status check and evolution in clinical practice since 2016. Intensive and Critical Care Nursing. 2025;89:103995.

4. Blair GJ, Mehmood T, Rudnick M, Kuschner WG, Barr J. Nonpharmacologic and medication minimization strategies for the prevention and treatment of ICU delirium: A narrative review. Journal of intensive care medicine. 2019;34(3):183-90.

5. LaHue SC, James TC, Newman JC, Esmaili AM, Ormseth CH, Ely EW. Collaborative delirium prevention in the age of COVID-19. Journal of the American Geriatrics Society. 2020;68(5):947.

6. Steardo L, Steardo Jr L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiologica (Oxford, England). 2020;229(3):e13473.

7. Steardo L, Zorec R, Verkhratsky A. Neuroinfection may potentially contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiologica. 2020 Jul;229(3):e13473. doi: 10.1111/apha.13473.

8. Lu Z, Wang X, Wang J, Zhao L, Wu Y, Sun M, et al. The intersection of delirium and long-term cognition in older adults: the critical role of delirium prevention. Journal of Neurology. 2025;272(6):1-19.

9. Ehler J, Petzold A. Haloperidol is not the "one drug fits all" solution in the treatment of delirium. Critical Care. 2025;29(1):163.

10. Glaess SS, Attridge RL, Christina Gutierrez G. Clonidine as a strategy for discontinuing dexmedetomidine sedation in critically ill patients: A narrative review. American Journal of Health-System Pharmacy. 2020;77(7):515-22.

11. Zolfaghari M, Arbabi M, Pedram Razi S, Biat K, Bavi A. Effectiveness of a multifactor educational intervention on delirium incidence and length of stay in patients with cardiac surgery. Journal of hayat. 2012;18(1):67-78.

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

12. Walsh TS, Parker RA, Aitken LM, McKenzie CA, Emerson L, Boyd J, et al. Dexmedetomidine-or clonidine-based sedation compared with propofol in critically ill patients: the A2B randomized clinical trial. JAMA. 2025. Advance online publication. https://doi.org/10.1001/jama.2025.7200

13. Baller EB, Hogan CS, Fusunyan MA, Ivkovic A, Luccarelli JW, Madva E, et al. Neurocovid: Pharmacological Recommendations for Delirium Associated With COVID-19. Psychosomatics. 2020;61(6):585-96.

14. Howard P, Curtin J. Efficacy and safety of subcutaneous clonidine for refractory symptoms in palliative medicine: a retrospective study. BMJ Supportive & Palliative Care. 2022;13(e3):e820-e4.

15. Wang JG, Belley-Coté E, Burry L, Duffett M, Karachi T, Perri D, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. Crit Care. 2017;21(1):75.

16. Hov KR, Neerland BE, Andersen AM, Undseth Ø, Wyller VB, MacLullich AMJ, et al. The use of clonidine in elderly patients with delirium; pharmacokinetics and hemodynamic responses. BMC Pharmacol Toxicol. 2018;19(1):29.

17. Recchia A, Tonti MP, Mirabella L, Izzi A, Del Gaudio A. The Pharmacological Class Alpha 2 Agonists for Stress Control in Patients with Respiratory Failure: The Main Actor in the Different Acts. Stresses. 2022;3(1):1-10.

18. Rowland DC, Waldvogel NJ. Clonidine for Management of Agitation in Delirious Patients. Current Psychiatry Reports. 2025:1-7. doi: 10.1007/s11920-025-01617-5.

19. Tang F, Ng CM, Horn J, Bada HS, Leggas M. Pharmacokinetic modeling and model-based hypothesis generation for dose optimization of clonidine in neonates with neonatal opioid withdrawal syndrome. Clinical Pharmacology & Therapeutics. 2025;117(5):1254-63.

20. Hanna J, Ghazi L, Yamamoto Y, Simonov M, Shah T, Wilson FP, et al. Excessive blood pressure response to clonidine in hospitalized patients with asymptomatic severe hypertension. American Journal of Hypertension. 2022;35(5):433-40.

Clinical Trial Registration Number:

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

This study was registered in the Iranian Registry of Clinical Trials (Code: IRCT20210425051075N2) on 2022-08-24, available at: https://irct.behdasht.gov.ir/trial/58290

Ethical Considerations:

This study was approved by the Research Ethics Committees of Sabzevar University of Medical Sciences (Code: IR.MEDSAB.REC.1400.072). It is worth noting that participation in this study was completely voluntary and after full awareness of the research aims and method and other treatment options. Also, informed written consent was obtained from the legal guardians of all patients before entering the study.

Funding:

This study was supported financially by the Sabzevar University of Medical Sciences (Code: 58290).

Conflict of interests:

The authors have no conflict of interest to declare.

Author contributions

All authors have read and agreed to the published version of the manuscript.

Conceptualization: Ahmadali Noorbala [1], Mohammad Arbabi [2], Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Writing—original draft preparation and project: Ahmadali Noorbala [1], Mohammad Arbabi [2], Houman Kamranian [3]

Administration: Ahmadali Noorbala [1], Mohammad Arbabi [2], Houman Kamranian [3]

Methodology: Ahmadali Noorbala [1], Mohammad Arbabi [2], Houman Kamranian [3]

Software: Ahmadali Noorbala [1], Mohammad Arbabi [2], Houman Kamranian [3]

Validation: Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Formal analysis and investigation: Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES

Resources and data curation:Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Visualization: Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Supervision: Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Writing—review and editing:Houman Kamranian [3], Zeinab Jalambadani [4], Asghar Kazemzadeh [5], Maliheh Lesaei [6], Mohammad Reza Shegarf Nakhaei [7]*

Funding acquisition: Mohammad Reza Shegarf Nakhaie [7*]

Esta obra está bajo licencia https://creativecommons.org/licenses/by-nc/4.0/deed.es_ES