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Dexmedetomidine for sedation and correction of psychoemotional disorders in critically ill patients with COVID-19

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ABSTRACT

Introduction. Most patients with COVID-19 require respiratory support and or mechanical ventilation, long-term use of high doses of sedatives, most of which should be considered in the context of the unique pathophysiology of COVID-19 and associated psychological and neurological disorders. Objective. The objective of this study was to evaluate sedation therapy effectiveness in critically ill patients with severe COVID-19 who received dexmedetomidine compared to propofol. Methods. The research was done in a prospective single center to a cohort study of critically ill 333 adult patients with COVID-19 and psychoemotional disorders (depression, anxiety and posttraumatic stress disorder) admitted in the ICU of the Republican Specialized Hospital for COVID-19 in Uzbekistan. Patients were non-invasive ventilated more than 24 hours and received intravenous sedation with dexmedetomidine or propofol. Results. The risk of progression of the pathological process decreased from 47.6% to 21.8% and, accordingly, the proportion of patients with stabilization and improvement of their condition increased from 52.4% to 79.4% ($p<0.001$). The possibilities of non-invasive respiratory support were expanded with a reduction in the frequency of tracheal intubations from 17.3% to 7.3% ($p<0.001$), the duration of ICU stay was from 12.6±0.8 to 9.4±0.6 days, and the duration of respiratory therapy was from 8.4±0.5 to 5.2±0.4 days. In particular, there was an improvement in oxygen saturation (SpO_2) recovery after one day of intensive therapy from 86.6±0.2% to 92.2±0.3% with non-invasive ventilation and a higher oxygenation index (2.3 in the dexmedetomidine group versus 1.6 in the propofol group, $p=0.032$) during the period of sedation withdrawal. Conclusion. In the presence of severe psychoemotional disorders, the effectiveness of etiotropic and pathogenetic treatment protocols of COVID-19 directly depends on the proper sedation regimen. In this aspect, dexmedetomidine provides adequate and safe respiratory support with an improvement in external respiration, blood gas composition and a minimal negative hemodynamic effect.

Original Article

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INTRODUCTION

The COVID-19 pandemic has become a global health problem, causing more than 167 million infections and more than 3.4 million deaths worldwide. According to the World Health Organization, "in most patients with COVID-19, with clinical manifestations, the disease is mild (40%) or has a moderate severity (40%), approximately 15% have pneumonia with the development of atypical acute respiratory distress syndrome, requiring respiratory support, and 5% have an extremely severe course with complications such as sepsis and septic shock, thromboembolism and/or multiple organ failure, including acute kidney and heart damage" [1]. Critically ill patients with COVID-19 are particularly at high risk of developing delirium, multiple organ failure and, as a consequence, intensive care unit syndrome [2]. Thus, more than 80% of patients with COVID-19 receiving treatment in intensive care units (ICU) have mental and neurological disorders, including sleep disorders, headache, dizziness, myalgia, anxiety and depression, delirium/encephalopathy, agitation, stroke, ischemic brain damage, seizures, coma and meningoencephalitis [3]. Preliminary results of retrospective cohort studies revealed that neurological manifestations of varying severity are often observed even in the absence of symptoms of respiratory failure [4].

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Most patients with COVID-19 require respiratory support and/or mechanical ventilation, long-term use of high doses of sedatives, most of which should be considered in the context of the unique pathophysiology of COVID-19 and associated psychological and neurological disorders. In addition, the long-term consequences of critical conditions in patients with COVID-19 who face the challenges of rehabilitation from cognitive disorders must be considered, which can significantly affect their quality of life [4, 5].

Dexmedetomidine, a sedative drug used in ICU, has a number of properties that may provide additional benefits to critically ill patients with COVID-19 who require sedation. The objective of this study was to evaluate sedation therapy effectiveness in critically ill patients with severe COVID-19 who received Dexmedetomidine compared to Propofol.

MATERIAL AND METHODS

The study included 333 adult patients (18 years old and older) with severe COVID-19 who were treated in the ICU of the Republican Specialized Zangiota-2 Hospital for COVID-19 in Tashkent region, Uzbekistan. Among the patients, the following psychoemotional disorders were identified: depressive syndrome, anxiety disorders, post-traumatic stress disorders (PTSD), as well as various options for their combination.

Upon arrival at the ICU, patients were randomized to either dexmedetomidine or propofol by continuous intravenous infusion under non-invasive ventilation and anesthesia, only when clinically necessary, with a morphine bolus. The initial intravenous of dexmedetomidine or propofol was given to rapidly achieve steady-state plasma concentration. The loading dose of infusion dexmedetomidine was 2.5 μg/kg/h for 10 minutes, followed by a maintenance infusion of 0.2-2.5 μg/kg/h into a peripheral vein. Propofol was given as an infusion of 1-3 mg/kg/h. Sedation was measured and recorded hourly using the Ramsay agitation sedation score (RASS) and patients were maintained at an RASS greater than 2 by adjusting the sedation regimen. No other sedatives or analgesics were used.

Patients underwent respiratory therapy using non-invasive mechanical ventilation with the achievement of acceptable blood gas content, and weaning from mechanical ventilation was carried out according to clinical indications. Sedation infusion was discontinued in preparation for ventilator shutdown, when the patient was alert, after reaching spontaneous breathing with pressure support (Ps) <10 cm H2O, tidal volume (Vt) > 6 ml/kg, and respiratory rate (RR) ≥ 10 and <25 breaths / min, and with arterial oxygen pressure (PaO2) ≥100 mm Hg. with an inhaled oxygen concentration (FiO2) <40% and had a PEEP <5 cm H_2O and with stable hemodynamics.

Heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2) were monitored continuously. Arterial blood samples were taken for blood gas analysis (pH, PaO2, PCO2, PaO2 / FiO2) immediately upon arrival at the ICU and then every 2 hours. Cardiovascular and respiratory adverse events were defined as a change in blood pressure ≥30% from baseline, bradycardia <55 beats/min, tachyarrhythmias, and respiratory rate <10 or >35 breaths/min after weaning from mechanical ventilation.

Statistical analysis

Data are shown as mean (M±m) values and comparisons were made using an unpaired t-test. Medians and interquartile range (IQR) are for skewed data, and comparisons were made using the Mann-Whitney U test, $p<0.05$ was considered significant. All analysis was performed using "Statistica" software for Windows.

Ethical approval

The research was conducted under a national process that obviated the need for approval.

RESULTS AND DISCUSSION

Analysis of the clinical course of psychoemotional disorders in patients with COVID-19 against the background of intensive therapy using sedation regimens (Table 1) showed that in the propofol group, in most cases, a combination of depressive syndrome, anxiety disorder and PTSD (12 of 17; 70.6%), the progression of the pathology was noted, while in the main group this indicator was 47.4% (9 of 19) without a statistical difference ($p=0.159$).

In the dexmedetomidine group, there was a relatively low percentage of cases with worsening general condition. A statistically significant difference in the indicators of improvement in the clinical picture of psychoemotional disorders (Table 1) was observed in cases of depressive syndrome ($p=0.028$), anxiety disorders

(p=0.018), PTSD (p=0.011), and in cases of a combination of depressive-anxiety disorders (p=0.032) and depression/PTSD (p=0.011). These results indicated that anxiety disorders and PTSD are the most difficult to treat types of psychoemotional disorders in resuscitation patients with COVID-19. In the dexmedetomidine group, the combined value of the proportion of progression of the psychologically complicated course of COVID-19 was 21.8% (36 of 165), which had a statistically significant difference (p<0.001) and was lower than in the propofol group - 47.6% (80 of 168).

Table 1. Distribution of patients with COVID-19 along the course of psychoemotional disorders during treatment

Condition		Improvement	Progression	Total
Propofol (n=168)				
Depression	n (%)	17 (70.8%)	7 (29.2%)	24 (14,3%)
Anxiety disorders	n (%)	25 (67.6%)	12 (32.4%)	37 (22%)
PTSD	n (%)	12 (60%)	8 (40%)	20 (11,9%)
Depression + anxiety disorders	n (%)	12 (44.4%)	15 (55.6%)	27 (16,1%)
Depression + PTSD	n (%)	5 (38.5%)	8 (61.5%)	13 (7,7%)
Anxiety disorders + PTSD	n (%)	12 (40%)	18 (60%)	30 (17,9%)
Depression + anxiety disorders + PTSD	n (%)	5 (29,4%)	12 (70,6%)	17 (10,1%)
Dexmedetomidine (n=165)				
Depression	n (%)	21 (95.4%)	1 (5.6%)	22 (13,3%)
	χ^2=4.843; p=0.028			
Anxiety disorders	n (%)	30 (91%)	3 (9%)	33 (20%)
	χ^2=5.644; p=0.018			
PTSD	n (%)	23 (92%)	2 (8%)	25 (15,2%)
	χ^2=6.583; p=0.011			
Depression + anxiety disorders	n (%)	19 (73.1%)	7 (26.9%)	26 (15,7%)
	χ^2=4.608; p=0.032			
Depression + PTSD	n (%)	9 (81.8%)	2 (18.2%)	11 (6,7%)
	χ^2=6.583; p=0.011			
Anxiety disorders + PTSD	n (%)	19 (65.5%)	10 (34.5%)	29 (17,6%)
	χ^2=3.851; p=0.05			
Depression + anxiety disorders + PTSD	n (%)	10 (52.6%)	9 (47.4%)	19 (11,5%)
	χ^2=1.990; p=0.159			

TSD: post-traumatic stress disorders.

There was no intergroup difference (p=0.15) in the time to reach and stay within the target sedation range (RASS score from -2 to +1). There was also no statistically significant difference (p=0.54) in the proportion of cases requiring interruption of study drug intake to maintain a RASS score from -2 to +1. At the same time, in the dexmedetomidine group, the average duration of sedation with the study drug was 4.2 days, while in the propofol group this indicator was 6.2 days (p=0.01). In terms of the time from the onset of sedation to weaning from noninvasive ventilation (NIV), a significant difference was obtained in favor of dexmedetomidine (4.6 vs. 7.6 days; p=0.01). Accordingly, the duration of ICU stay was reduced from 12.6 to 9.4 days (p=0.028). Dexmedetomidine sedation was found to be more effective in preventing delirium. Thus, in the main group, the frequency of this complication was 43.0% versus 67.2% in the propofol group (p<0.001). The addition of morphine to sedation was required in 65.8% of patients in the dexmedetomidine group and 91.7% in the propofol group (p<0.001).

In the dexmedetomidine group, the rate of tracheal intubation was 7.3% (12 of 165), while in the propofol group, the rate was 17.3% (29 of 168). The frequency of intubations was higher in the propofol group and in the early stages of treatment - days 1-2 - 5.36% (dexmedetomidine - 1.8%), on days 3-4 - 2.4% versus 1.2%, and more late (7-8 days, more than 9 days) periods of stay of patients in the ICU - 5.36% versus 1.8%.

The duration of treatment in the ICU in patients with depressive syndrome was reduced from 8.5±0.5 to 7.3±0.6 (t=-2.18; p<0.05), with anxiety disorders from 9.5±0.6 to 8.2±0.5 (t=-3.54; p<0.05), and in cases of PTSD from 10.4±0.8 to 8.8±0.5 days (t=-2.86; p<0.05); also in an extremely severe course of psychoemotional disorders with a combination of syndromes, a statistically significant difference was noted in favor of the dexmedetomidine group. On average, the duration of treatment in the ICU in the propofol group was 12.6±0.8 days, while in the dexmedetomidine group it was 9.4±0.6 (t=-2.89; p<0.05). The duration of the stay of patients on NIV was also statistically significantly less during sedation with dexmedetomidine, amounting to 5.2±0.4 versus 8.4±0.5 days in the propofol group (t=-5.20; p<0.05).

Baseline RR (respiratory rate) were comparable with no statistical difference. Subsequently, 3 hours after the administration of the loading dose of the drug and reaching the target depth of sedation, the average RR was 33.7±0.8 per minute in the propofol group and 31.1±0.8 in the dexmedetomidine group. Further, a similar trend was also recorded with a significant intergroup difference. So, after 6 hours the RR was within 28±0.9 per minute. with sedation with propofol, while against the background of the sedative effect of dexmedetomidine - 25.2±0.8 per minute (t=-2.52). Respiratory rate within the normal range (19.2±0.7 per minute) was achieved only 24 hours later with dexmedetomidine sedation, while in the propofol group for this period, the average RR was noted from 22.4±0.8 per minute (t=-3.47).

As can be seen from Figure 1 mean values of RR against the background of NIV and sedation with dexmedetomidine for the 6-hour period before the sedation was switched off had a statistically significant difference compared with similar indicators in the propofol group, whereas there were no statistically significant differences between the propofol groups within 6 hours after the sedation was switched off and dexmedetomidine (p=0.37).

The initially studied groups were comparable according tidal volume (Vt) to this criterion (t=-0.28). Subsequent comparative evaluation showed that statistically significant differences in Vt (t=2.14; p<0.05) were obtained as early as 6 hours after the onset of development and amounted to 4.6±0.2 ml/kg in the dexmedetomidine group versus 3.4±0.2 ml/kg. Then, one day later, the Vt was 5.8±0.2 and 4.6±0.2 ml/kg in the group of dexmedetomidine and propofol, respectively, with an intergroup difference (t=3.18; p<0.05). In the analysis of the mean Vt for the 6-hour period before and after sedation withdrawal, the studied indicator was higher in the dexmedetomidine group, but statistically significant intergroup differences were not obtained.

During sedative therapy of psychoemotional status disorders in severe COVID-19 blood saturation (SpO_2), measured by pulse oximetry, was increased from the initial 44.6±1.4% to 84.6±0.2% after 24 hours after the start of therapy in the propofol group and from 43.2±1.4% to 88.2±0.3% in the dexmedetomidine group (t=7.64; p<0.05).

After disabling sedation for 6 hours, the mean saturation values were higher in the dexmedetomidine group with a statistically significant difference (p<0.05), which meant a more effective effect of the study drug in the treatment of psychoemotional disorders affecting the quality of respiratory therapy in patients with COVID-19 (Figure 3). At the same time, in both study groups, the target oxygen saturation range (92-96%), established for patients with COVID-19, and recommended by the National Institutes of Health was achieved [5].

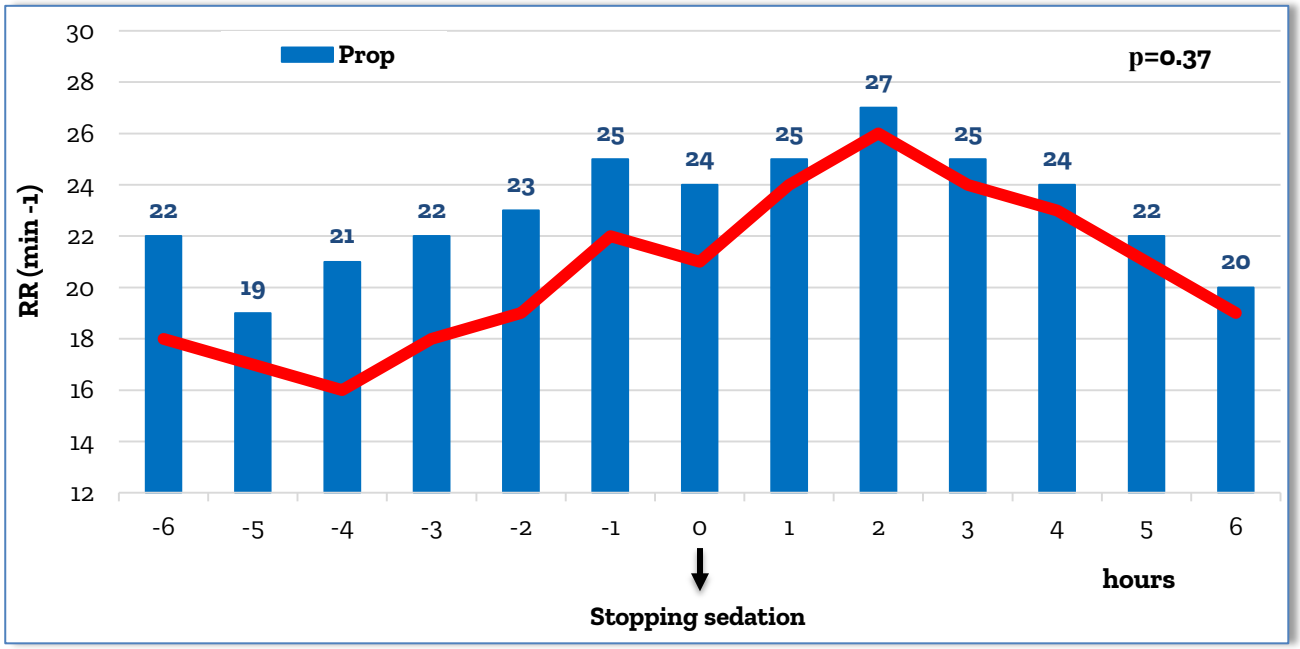

Figure 1. Comparative dynamics of the average values of RR against the background of NIV for a 6-hour period before and after disabling sedation

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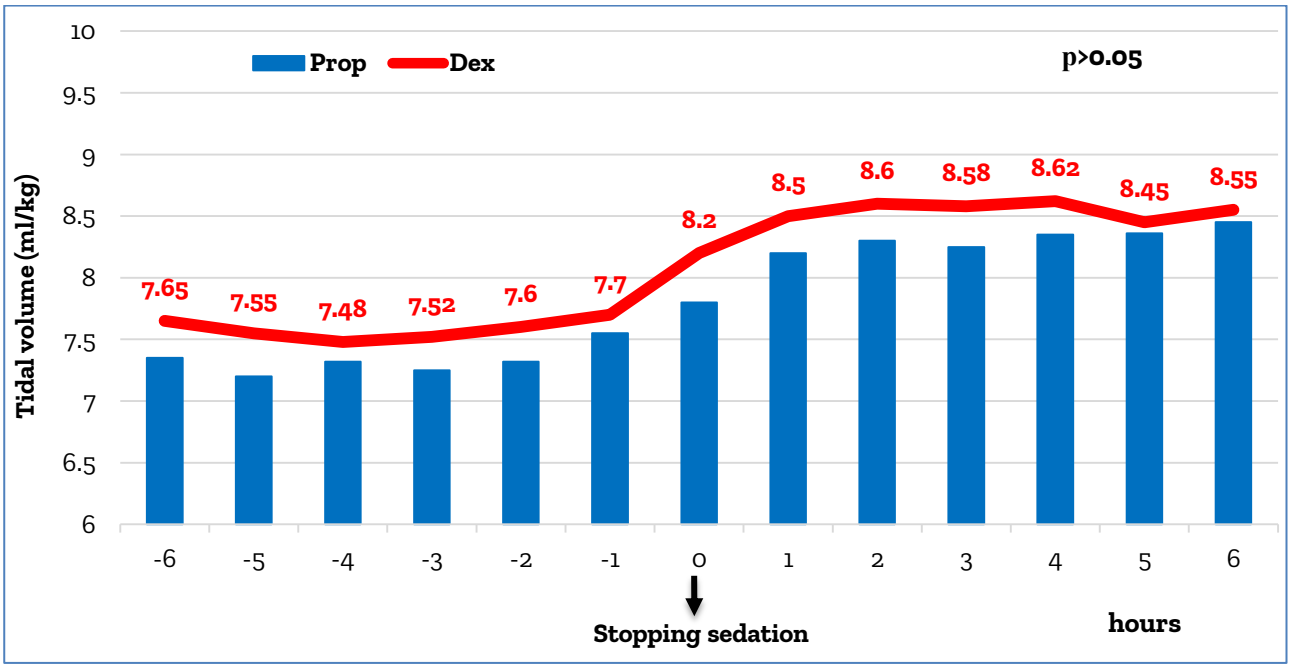

Figure 2. Comparative dynamics of the mean values of Vt (ml/kg) against the background of sedation and NIV for a 6-hour period before and after disabling sedation

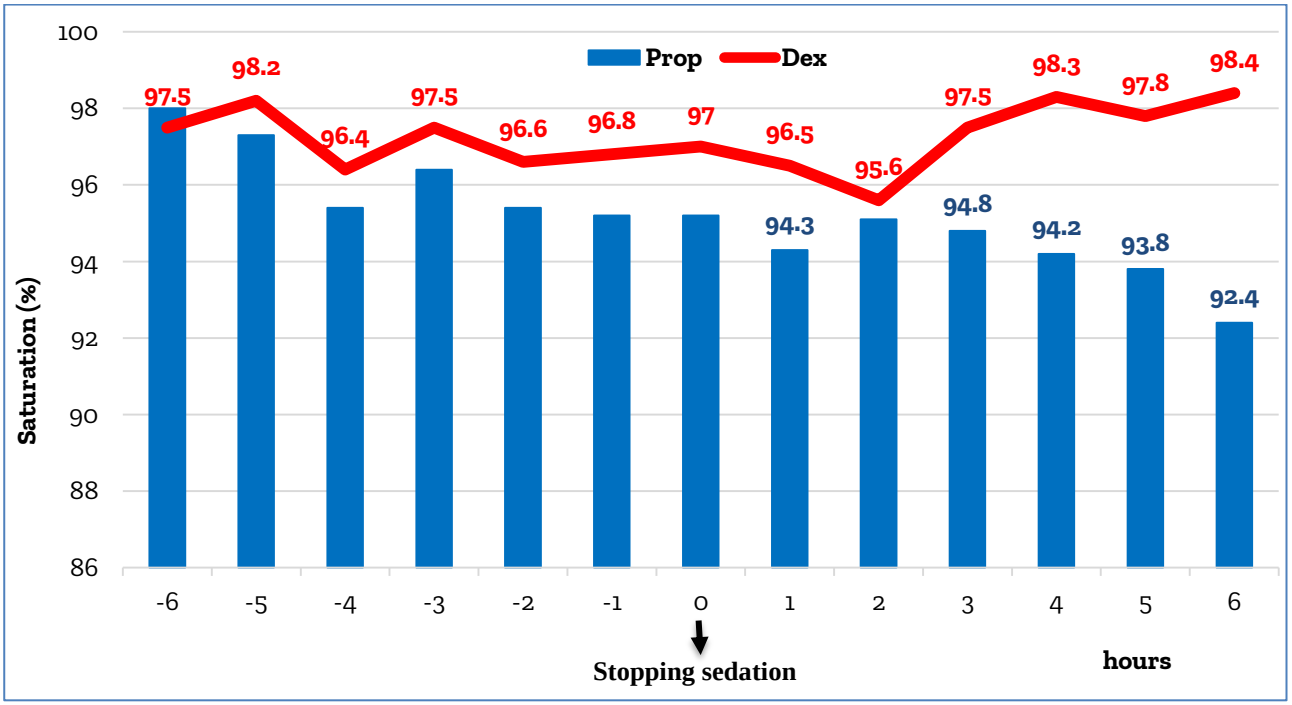

Figure 3. Comparative dynamics of the average values of saturation (%) of blood against the background of NIV for a 6-hour period before and after disabling sedation

The study also examined the therapeutic effects of dexmedetomidine and propofol on arterial blood gases and the correction of acid-base balance. It is known that in the majority of the studied population admitted to the ICU, alkalemia is detected by arterial and venous blood gases with an increase in HCO_3^- and pCO_2. At the same time, it is noted that higher pH and pO_2 are significantly associated with survival. In our study, we found no statistically significant difference between the propofol and dexmedetomidine groups in arterial pH (p=0.74) and $PaCO_2$ (p=0.62) between groups during the 6-hour period after sedation was withdrawn.

The dexmedetomidine group showed significantly higher oxygenation index (PaO_2/FiO_2) values for 6 hours before cessation of sedation (p=0.032) and after (p=0.028). No adverse respiratory events were observed in either the dexmedetomidine group or the propofol group. In both groups with an initial tachycardia characteristic of hypoxic conditions and systemic inflammatory response syndrome, the heart rate decreased to normal values only a day after the start of treatment. At the same time, a more pronounced effect of sedation

was noted in the dexmedetomidine group, but without a transition to bradycardia, which is important and excludes the negative hemodynamic effect of the dexmedetomidine.

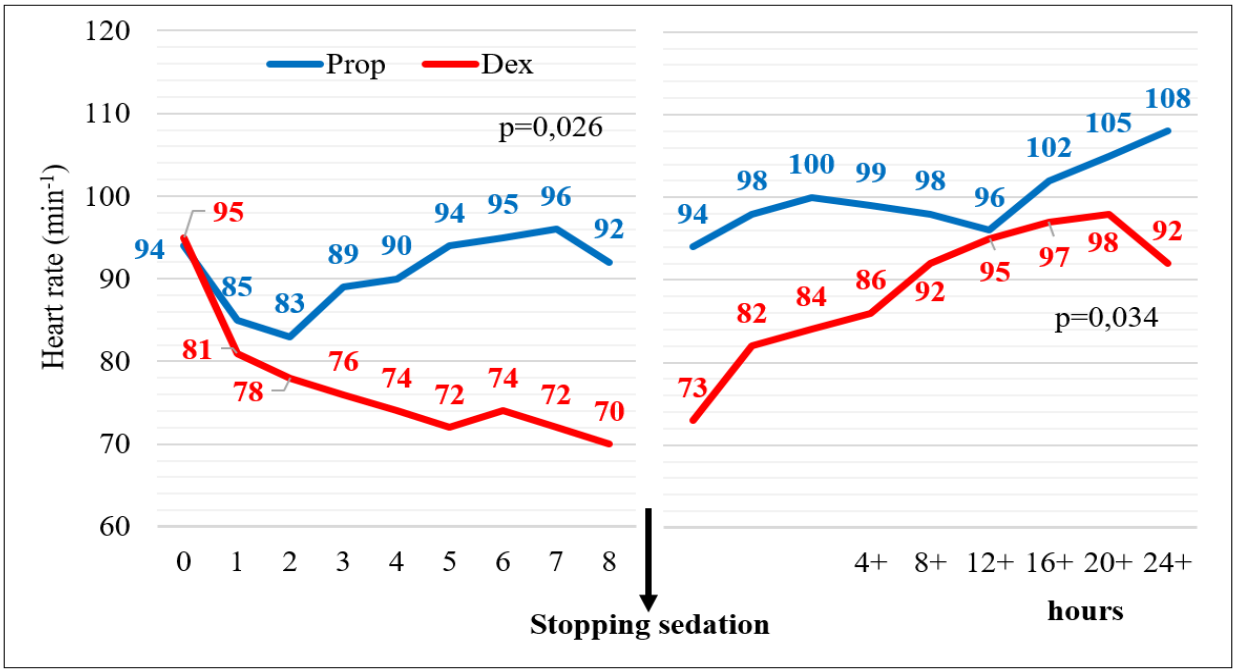

Fig. 4. Comparative dynamics of the average values of HR (min^{-1}) against the background of NIV before and after disabling sedation

In patients treated with dexmedetomidine, the HR was significantly lower than in the propofol group both before sedation deactivation (p=0.026) and after it (p=0.034), which could mean a more pronounced therapeutic effect of dexmedetomidine in providing and maintaining hemodynamic stability during the use of NIV in patients with COVID-19 (Figure 4). There were no differences in systolic and diastolic blood pressure between the two groups (p = 0.60) during and after sedative infusion. No patient required inotropes, and none of the groups had adverse cardiovascular events (Figure 5).

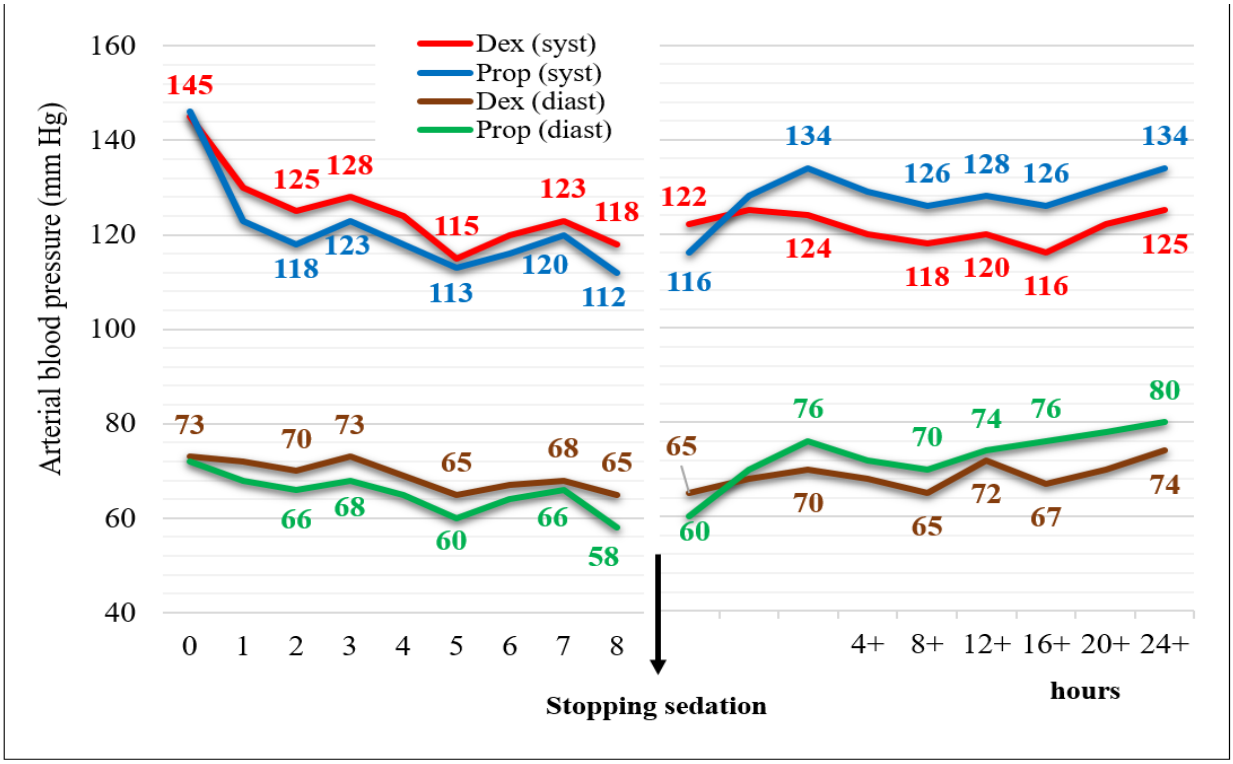

Figure 5. Mean values of systolic and diastolic blood pressure (mm Hg) against the background of NIV before and after disabling sedation

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DISCUSSION

There is limited information available on risk factors and mechanisms for the development of mental health problems among patients with COVID-19. Patient factors such as increased dyssynchrony between the ventilator, the need for a higher positive end-expiratory pressure, restlessness and anxiety in the patient could contribute to the use of deeper sedation [6, 7]. Current protocols call for limiting deep sedation, which worsens the short- and long-term prognosis of COVID-19 pneumonia, and carries risks such as hemodynamic instability and prolonged mechanical ventilation [8, 9]. In this aspect, dexmedetomidine can be considered as the most acceptable drug capable of providing mild sedation and having an opioid-sparing effect.

Propofol, containing 0.1 g of fat in 1 ml, can cause hypertriglyceridemia, which requires control of triglyceride levels in patients who continue to take propofol [10]. It is recommended that non-propofol sedation strategies be considered when triglyceride levels are greater than 500 mg/dL. In addition, patients with COVID-19 may have a picture of secondary hemophagocytic lymphohistocytosis, which is the result of over-activation of the immune system and inflammation, which leads to tissue destruction and high mortality [11].

Benzodiazepines are less commonly used as sedatives because of the increased risk of delirium and ICU syndrome. It is known that midazolam has a prolonged sedative effect with prolonged use and accumulates in patients with renal or hepatic dysfunction, heart failure or obesity [12-15].

At the onset of a pandemic, it was reported that patients with COVID-19 received sedatives for a long time: two thirds of patients received benzodiazepines and propofol for an average of 7 days [16]. It was found that the risk of delirium among patients with severe COVID-19 was lower when benzodiazepine sedative infusions were avoided, while greater disease severity and greater respiratory support were associated with a higher risk of delirium [17].

In conditions of drug shortages, oral forms of diazepam or lorazepam can be used periodically to minimize the need for sedative infusion therapy [18, 19]. A recent meta-analysis of randomized controlled studies suggests that dexmedetomidine could help to reduce delirium in critically ill patients [18]. Dexmedetomidine could be the preferred sedative agent for patients who have noninvasive ventilation (NIV) intolerance due to agitation. Meta-analysis of randomized controlled trials showed that clinical outcomes of dexmedetomidine use in NIV were encouraging, though further prospective studies are needed to confirm these results [19].

Results of this study showed that the primary assessment of the severity of psychoemotional disorders using special scales in patients with severe COVID-19 and sedation therapy with dexmedetomidine reduced the risk of progression of the pathological process from 47.6% to 21.8%, and expanded the possibilities of non-invasive respiratory support, reduce the frequency of tracheal intubations from 17.3% to 7.3% and reduce the duration of resuscitation treatment from 12.6±0.8 to 9.4±0.6 days.

CONCLUSION

In the presence of severe psychoemotional disorders, the effectiveness of the etiotropic and pathogenetic treatment of COVID-19 (correction of coagulopathy, respiratory and antibiotic therapy) directly depends on the proper sedation regimen. In this aspect, dexmedetomidine provides adequate and safe respiratory support with an improvement in external respiration, blood gas composition and minimal negative hemodynamic effect.

DECLARATIONS

Acknowledgments

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Authors' Contributions

All authors contributed equally to this work.

Competing interests

The authors declare that they have no competing interests.

REFERENCES

1. World Health Organization. COVID-19 clinical management: living guidance (25 January 2021). Google Scholar
2. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020; 382:2268-70. PMID: 32294339 ; PMCID: PMC7179967 ; DOI: https://doi.org/10.1056/NEJMc2008597
3. Favas TT, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurol Sci. 2020; 41(12):3437-3470. PMID: 33089477; PMCID: PMC7577367 ; DOI: https://doi.org/10.1007/s10072-020-04801-y
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77(6):683-690. PMID: 32275288 ; PMCID: PMC7149362 ; DOI: https://doi.org/10.1001/jamaneurol.2020.1127
5. Shenoy N, Luchtel R, Gulani P. Considerations for target oxygen saturation in COVID-19 patients: are we under-shooting? BMC Med. 2020; 18(1):260. PMID: 32814566 ; PMCID: PMC7437106; DOI: https://doi.org/10.1186/s12916-020-01735-2
6. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep; 19(9):767-783. PMID: 32622375 PMCID: PMC7332267 ; DOI: https://doi.org/10.1016/S1474-4422(20)30221-0
7. Kotfis K, Roberson SW, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Critical care. 2020 Dec; 24(1):1-9. PMID: 32345343 ; PMCID: PMC7186945 ; DOI: https://doi.org/10.1186/s13054-020-02882-x
8. Karamchandani K, Dalal R, Patel J, Modgil P, Quintili A. Challenges in Sedation Management in Critically Ill Patients with COVID-19: a Brief Review. Curr Anesthesiol Rep. 2021; 26:1-9. PMID: 33654458 ; PMCID: PMC7907309; DOI: https://doi.org/10.1007/s40140-021-00440-x
9. Hanidziar D, Bittner EA. Sedation of Mechanically Ventilated COVID-19 Patients: Challenges and Special Considerations. Anesth Analg. 2020 Jul; 131(1):e40-e41. PMID: 32392023 ; PMCID: PMC7179055 ; DOI: https://doi.org/10.1213/ANE.0000000000004887
10. Devaud JC, Berger MM, Pannatier A, Marques-Vidal P, Tappy L, Rodondi N, Chiolero R, Voirol P. Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness. Intensive Care Med. 2012 Dec; 38(12):1990-8. PMID: 23052949 ; DOI: https://doi.org/10.1007/s00134-012-2688-8
11. Meng M, Chen L, Zhang S, Dong X, Li W, Li R, Deng Y, Wang T, Xu Y, Liu J, Huang Y, Chen Y, Huang S, Wen Z, Zhang L, Du H, Liu Y, Annane D, Qu J, Chen D. Risk factors for secondary hemophagocytic lymphohistiocytosis in severe coronavirus disease 2019 adult patients. BMC Infect Dis. 2021 Apr 29; 21(1):398. PMID: 33926377 ; PMCID: PMC8084265 ; DOI: https://doi.org/10.1186/s12879-021-06094-8
12. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006 Jan; 104(1):21-6. PMID: 16394685 ; DOI: https://doi.org/10.1097/00000542-200601000-00005
13. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14; 291(14):1753-62. PMID: 15082703 ; DOI: https://doi.org/10.1001/jama.291.14.1753
14. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. N Engl J Med. 2013 Oct 3; 369(14):1306-16. PMID: 24088092 ; PMCID: PMC3922401 ; DOI: https://doi.org/10.1056/NEJMoa1301372
15. Lonardo NW, Mone MC, Nirula R, Kimball EJ, Ludwig K, Zhou X, Sauer BC, Nechodom K, Teng C, Barton RG. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. Am J Respir Crit Care Med. 2014 Jun 1;1 89(11):1383-94. PMID: 24720509 ; DOI: https://doi.org/10.1164/rccm.201312-2291OC
16. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May; 8(5):475-481. PMID: 32105632 ; PMCID: PMC7102538 ; DOI: https://doi.org/10.1016/S2213-2600(20)30079-5
17. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med. 2021 Mar; 9(3):239-250. DOI: https://doi.org/10.1016/S2213-2600(20)30552-X ; PMID: 33428871; PMCID: PMC7832119.
18. Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2014 Dec; 28(6):1459-66. PMID: 25034724; DOI: https://doi.org/10.1053/j.jvca.2014.03.010
19. Ju T, Lee CC, Chen WC, Lin HT. Use of dexmedetomidine in critically ill patients receiving noninvasive ventilation: a meta-analysis of randomized controlled trials. Chest. 2020; 158(4):A577. DOI: https://doi.org/10.1016/j.chest.2020.08.545