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Effects of Dexmedetomidine and Propofol on Hemodynamic Stability and Ventilation Time in Patients Suffering COVID-19 Admitting to Intensive Care Units

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ABSTRACT

Background: The introduction of novel analgesics such as dexmedetomidine could pave the way for patient relaxation as well as hemodynamic stability more successfully. Such successful achievement can be very essential in critically ill patients suffering acute life-threatening events. We examined the ability of dexmedetomidine in stabilizing hemodynamic parameters as well as shortening ventilation time in critically ill patients suffering COVID-19 disease admitting to ICUs.

Methods: The present randomized double-blinded controlled trial was conducted on 46 consecutive adults aged 35 to 50 years suffering COVID-19 and admitted to ICU at a referral hospital in Iran for COVID-19 patients. All included patients were mechanically ventilated with the similar protocol and were randomly assigned into two groups receiving dexmedetomidine (0.8 μg/kg/h) as the intervention group and propofol (1.5 mg/ kg/h) as the control group.

Results: Comparing the changes in vital signs within 12 hours of study interventions showed the decrease in heart rate and mean arterial pressure along with increase in arterial oxygen saturation in both groups, however the trend of the change in heart rate and mean arterial pressure was significantly different across the two groups as more stability of such vital parameters in

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dexmedetomidine group. The time for mechanical ventilation for dexmedetomidine and propofol groups was 29.12±4.87 hours and 33.20±4.22 hour respectively indicating shorter time for ventilation required in dexmedetomidine group (p = 0.003).
Conclusion: The use of dexmedetomidine as compared to propofol leads to more hemodynamic stability as well as shorter ventilation time.
Keywords: COVID-19, Dexmedetomidine, Ventilation,Hemodynamic, Intensive Care Units

INTRODUCTION

Mechanical ventilation as a central process for managing critically ill patients is very vital, but very complex. Both considering from the ventilation and weaning of the ventilator should be done according to standard principles with the goal of stabilizing the hemodynamic along with minimizing its-related complications [1,2]. In this regard, the time for ventilation not only has been accepted as a major factor affecting the patients' outcome, but also is considered as an index for appropriately managing the patients such as needing discharging or transferring the patients to the ward [3,4]. In this regard, prolonged ventilation in intensive care units (ICU) may increase the likelihood of postoperative adverse events, increase healthcare costs, and also decrease the ICU beds availability [5,6].

Along with the necessity for mechanical ventilation in candidate patients, the use of sedative and analgesic medications is necessary for most patients to improve the tolerance to the procedure, relaxation while using this tool, effective use of simultaneous invasive procedures, stabilizing the hemodynamic parameters, and reduce the level of stress and anxiety [7]. In this context, two types of sedatives including opioid analgesics and hypnotic agents are used with this aim. Benzodiazepines are initially sedatives applied for sedating patients under mechanical ventilation however due to the risk for hemodynamic instability and fluctuation, their use was limited [8]. The application of intravenous opioids has been also less popular because of potential risky conditions such as exacerbation of respiratory depression as well as extubation failure [9]. Recently, the use of dexmedetomidine for sedating critically ill patients under mechanical ventilation has received special attention [10]. Significant superiority of this agent over other materials is to provide hemodynamic stability as well as no significant effect on respiratory pattern [11]. These characteristics may be more important and vital in patients with high risk for respiratory distress and impaired arterial oxygen saturation. Moreover, the minimal effect of dexmedetomidine on cognitive condition of the patients has been also pointed [12]. In the present study, we examined the ability of dexmedetomidine in stabilizing hemodynamic parameters as well as shortening ventilation time in critically ill patients suffering covid-19 disease and admitting to ICUs. We selected such patients in our trial due to numerous reports of severe instability in the respiratory pattern and the level of consciousness of patients with the disease.

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MATERIAL AND METHODS

Study population

The present randomized double-blinded controlled trial was conducted on 46 consecutive adults aged 35 to 50 years suffering COVID-19 and admitted to ICU at a referral hospital for such patients in Iran between February and April 2020. The definitive diagnosis of the disease was made on the basis of a dedicated COVID-19 diagnostic kit and RT-PCR of the virus genome in the laboratory (isolation of SARSCoV-2 or at least two positive tests of the genomic virus test). In our trial, all patients with COVID-19 that were candidate for admitting ICU and requiring mechanical ventilation were included into the study. The principal scheme for deciding admission of patients with COVID-19 to ICUs is described by Bouadma et al [13]. The main indications for mechanically ventilating such patients were as follows: 1) failure to maintain a patent airway due to decreased level of consciousness, requiring deep sedation, upper airway obstruction due to edema, trauma, or hematoma, edema, inability to manage secretions, 2) failure to maintain adequate ventilation; and 3) failure to maintain adequate oxygenation. As the exclusion criteria, those with chronic kidney or liver diseases, evidences of neurological or cognitive disturbances, history of ischemic heart disease or significant cardiac arrhythmias, bradycardia (heart rate less than 50 beats per minute, persistent hypotension (systolic blood pressure <90 mmHg), administrating anticonvulsant medications, pregnancy or lactation, andallergy to dexmedetomidine or propofol were excluded. A written informed consent was taken from all eligible patients entering the trial.

Study interventions and measurements

By admitting to ICUs, all included patients were mechanically ventilated with the similar protocol with a tidal volume of 8 to 10 mL/kg of body weight. To achieve a partial stable arterial oxygen pressure ranged 80 to 100 mmHg and partial arterial CO2 pressure of ranged 35 to 40 mmHg, the FIO2 and respiratory rate were adjusted to arterial blood gas analysis. Thereafter, the patients were randomly assigned (using the simple random table) into two groups receiving dexmedetomidine (0.8 μg/kg/h) as the intervention group and propofol (1.5 mg/ kg/h) as the control group. For depressing agitation or delirium within interventions, haloperidol (up to 5 mg, repeated every 10 to 20 min) were considered. Looking to effective spontaneous breathing without ventilator assistance, the extubation and weaning of ventilator were ordered and the time between connection to ventilator and extubation was determined. In addition to assessing time to extubation and weaning of ventilation, hemodynamic status based on measuring heart rate, respiratory rate, blood pressure and arterial oxygen saturation were also repeatedly measured every 4 hours within first 24 hours of hospitalization.

Statistical analysis

The results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups.

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Categorical variables were, on the other hand, compared using chi-square test. The multivariable linear regression model was employed to assess the difference in quantitative parameters across the intervention and control groups. P values of ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 24.0 for windows (IBM, Armonk, New York) was used.

RESULTS

In the present trial, 25 patients were planned for injecting dexmedetomidine (n = 25) and 25 for injecting propofol (n = 25). As shown in Table 1 with respect to baseline characteristics, there was no difference in baseline parameters including demographics, medical history, clinical manifestations and hemodynamic indices on admission as well as mean ICU stay. Comparing the changes in vital signs within 12 hours of study interventions (Figures 1 to 3) showed the decrease in heart rate and mean arterial pressure along with increase in arterial oxygen saturation in both groups, however the trend of the change in heart rate and mean arterial pressure was significantly different across the two groups as more stability of such vital parameters in dexmedetomidine group as compared to propofol group. The time for mechanical ventilation for dexmedetomidine and propofol groups was 29.12±4.87 hours and 33.20±4.22 hour respectively indicating shorter time for ventilation required in dexmedetomidine group (p = 0.003). In a multivariable linear regression model (Table 2) with the presence of baseline variables, the difference in mean ventilation time between the two interventional groups remained significant after adjusting baseline variables.

Table 1: Comparing baseline variables between the two groups

Item	Dexmedetomidine (n = 25)	Propofol (n = 25)	P value
Male gender	17 (68.0)	15 (60.0)	0.556
Mean age, year	55.64±7.84	55.72±5.65	0.967
Mean BMI, kg/m^2	25.44±2.14	25.48±2.50	0.952
History of hypertension	8 (32.0)	9 (36.0)	0.765
History of diabetes mellitus	5 (20.0)	5 (20.0)	1.000
History of ischemic heart disease	3 (12.0)	3 (12.0)	1.000
Mean ICU stay, day	8.44±1.76	7.72±1.99	0.720
Fever	16 (64.0)	18 (72.0)	0.544
Cough	10 (40.0)	14 (56.0)	0.258
Fatigue	5 (20.0)	8 (32.0)	0.333
Mean heart rate, per minute	83.72±7.78	82.56±5.79	0.553
Respiratory rate, per minute	18.20±1.15	18.08±1.15	0.120
Mean SBP, mmHg	141.40±15.51	144.40±14.74	0.478
Mean DBP, mmHg	85.00±9.46	88.80±6.50	0.104
Mean temperature, °C	38.05±0.65	38.00±0.69	0.802
Mean oxygen saturation, %	85.28±2.73	85.76±2.47	0.518

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Mean WBC count, per mm^3	4.93±0.59	5.21±0.89	0.206
Mean lymphocyte count, per mm^3	1.57±0.41	1.56±0.30	0.843
Mean ESR	100.24±11.08	101.84±10.87	0.609
Mean CRP	10.88±4.23	10.80±4.00	0.951

Table 2: The multivariable linear regression model to assess the difference in ventilation time

Item	Unstandardized Coefficients		Standardized Coefficients	t	P value
	Beta	Std. Error	Beta		
(Constant)	20.230	12.508		1.617	0.115
group	4.396	1.324	0.448	3.321	0.002
Gender	0.467	1.497	0.046	0.312	0.757
age	0.068	0.103	0.093	0.664	0.511
BMI	0.490	0.306	0.228	1.603	0.118
HTN	-0.929	1.628	-0.090	-0.571	0.572
DM	-5.614	2.927	-0.457	-1.918	0.063
CHD	3.769	3.565	0.250	1.057	0.298
fever	-0.116	1.641	-0.011	-0.071	0.944
cough	-0.801	1.437	-0.082	-0.557	0.581
fatigue	-0.310	1.614	-0.028	-0.192	0.849
WBC	-2.056	0.987	-0.318	-2.082	0.045
lymph	2.542	1.937	0.184	1.312	0.198
ESR	0.014	0.062	0.031	0.225	0.824
CRP	-0.099	0.170	-0.082	-0.585	0.563

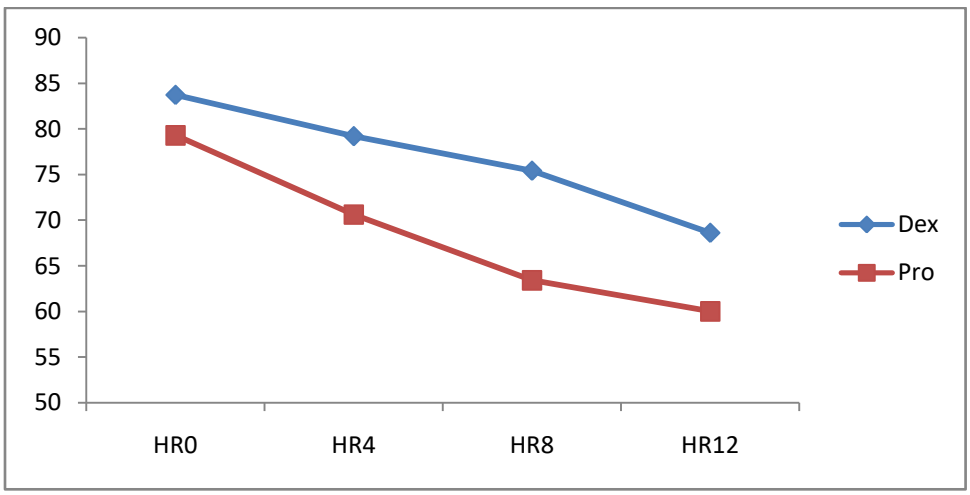

Figure 1: The trend of the change in heart rate within 12 hours of intervention

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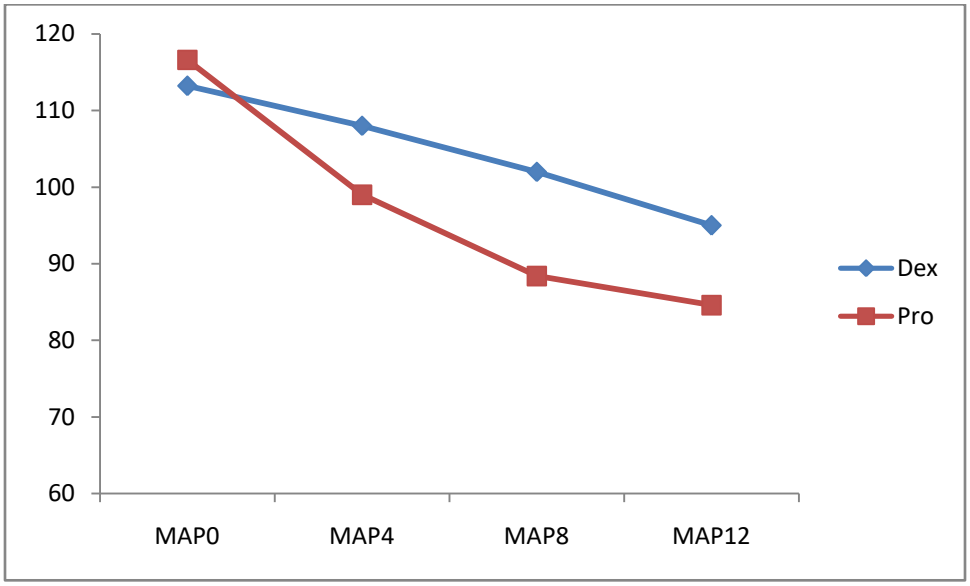

Figure 2: The trend of the change in mean arterial pressure within 12 hours of intervention

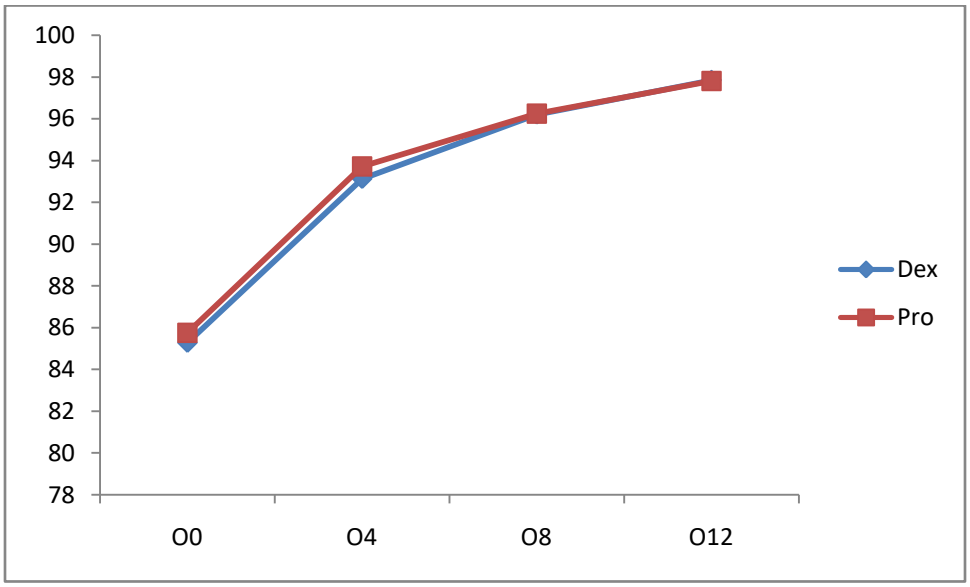

Figure 3: The trend of the change in O2 saturation within 12 hours of intervention

DISCUSSION

Patients who are admitted to ICUs and require intensive care should be set on a relieving pain control managements due to the painfulness nature of the underlying disease and its complications and also to requirement of some invasive or semi-invasive critical cares such as mechanically ventilation. Such managements can also prevent delirium, agitation, and hemodynamic instability that are frequently as the results of responses to pain. According to reported sourced from ICUs, more than half of the patients admitting to ICUs need to pain management. Such patients can also not communicate for setting mechanical ventilation. Thus,

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critically ill patients who are unable to cooperate with the ventilation agency should be prescribed various types of analgesics leading more proper ICU-related outcomes such as shorter ICU stay, lower suffering agitation and delirium, maintaining hemodynamic stability and also reducing in-hospital death. However, the condition for achieving such a result is that the analgesic drugs used do not lead to hemodynamic instability or serious drug side effects. Some previous analgesics and sedatives such as opioids and hypnotic, in spite of their effectiveness, themselves interfered with the clinical implications of patients. The introduction of novel analgesics such as dexmedetomidine could pave the way for patient relaxation along with patient hemodynamic stability. Such successful achievement can be very essential in critically ill patients suffering acute life-threatening events. In this regard, we attempted to examine the efficacy of dexmedetomidine in comparison with an older sedative agent, propofol, in pain management of patients admitted to ICUs with the definitive diagnosis of severe COVID-19 disease. Due to its unknown nature and course, this disease has always been associated with fear among infected patients, so controlling the pain and sedation of infected patients in its severe condition can play a significant role in their therapeutic outcome.

We could well show first that the use of dexmedetomidine, not only help to stability of patients' hemodynamic, but also could reduce the time for requiring mechanical ventilation and thus the intubation time was also significantly reduced. Our study was the first trial on the clinical efficacy of dexmedetomidine for sedation and reducing time for ventilation in COVID-19 patients, thus emphasizing its high safety and effectiveness among such patients. In a study by Elgebaly et al in 2018 [14], although there was no significant difference between the two groups receiving dexmedetomidine and propofol in terms of arterial blood gas parameters, oxygenation, ventilation, and respiratory parameters, groups receiving propofol were more associated with lower mean arterial pressure and heart rate than another group. In a study by Shehabi et al in 2010 [15], dexmedetomidine achieved rapid resolution of agitation and facilitated ventilatory weaning by successful weaning from ventilation with reducing ventilation time in more than two-third of patients. In a trial by Song et al in 2015 [16], both dexmedetomidine and midazolam could give rise to sedation with same score of analgesia, but compared with midazolam, dexmedetomidine could significantly reduce the duration of mechanical ventilation and led to earlier extubation time, length of ICU stays, and the incidence of delirium. Gupta et al [17] also indicated that although the time to extubation in the dexmedetomidine group was significantly lower than in the midazolam group, but reflexively, heart rate and blood pressure was significantly lower in dexmedetomidine group than the midazolam group at most of the times. Contrarily, some authors could not indicate the superiority of dexmedetomidine to other analgesics specially to provide patients' satisfaction. As shown by Corbett et al in 2005 [18], although dexmedetomidine patients perceived a shorter length of intubation as compared to propofol group, dexmedetomidine patients expressed more discomfort, pain, and sleeping difficulty. In general, although the results of studies may be quite different due to the type of study design, the power of the study, the type and severity of the underlying disease, as well as

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the experience of the treating physician, according to our study results, dexmedetomidine use can be preferred to other sedative methods due to hemodynamic stability as well as reduced ventilation time.

CONCLUSION

According to our clinical trial, due to more appropriate hemodynamic stability as well as shortening the time of ventilation required, the use of dexmedetomidine is preferred to other analgesics such as propofol in patients suffering COVID-19 needing intensive cares.

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AUTHORS' CONTRIBUTIONS

All authors have done substantial contributions to conceptionand design. kGh collected, analysed and interpreted the data. MMF, NN and FS analysed and interpreted the data. MM was the main writer of the manuscript. MRA, AD, SSK, PD, RFR and SA made important intellectual contributions to the manuscript. All authors read and approved the final manuscript.

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