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Original Article

Role Of Dexmedetomidine By Improving Sleep Quality And Pain Control In Covid-19 Patients

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Abstract

OBJECTIVE: To demonstrate the effective role of Dexmedetomidine as a sedative and analgesic agent in Covid-19 patients when used in conjunction with the established treatment of acute respiratory distress syndrome.

INTRODUCTION: Covid-19 disease is a deadly contagious disease with milder symptoms to a more severe form with acute respiratory failure, and septic shock leading to even death. Literature study shows High Flow Nasal Oxygen therapy and prolonged prone position sessions to be beneficial in the treatment of ARDS, however, to facilitate those sessions, a sedative and anxiolytic agent must be added to the treatment. Therefore, this study was conducted to document the beneficial role of dexmedetomidine as a sedative agent.

METHODOLOGY: Retrospective observational study which included 150 PCR-positive patients admitted in Covid ITC, from 1st February 2021 to 31st July 2021 residing in the premises of PAF Air Base, Mushaf, Sargodha. Data were analyzed using SPSS software.

RESULTS: Out of 150 patients, 120 (80%) were treated with High Flow Nasal Oxygen (HFNO), Dexmedetomidine infusion (DEXME), and long periods of prone position (PP) sessions. Among these 120 patients, 88 (73.3%) were discharged while 32 (26.67%) patients died of which 7 (21.875%) died while being on HFNO therapy and 25 (78.125%) patients were intubated. DEXME infusion was found to have a positive outcome (P-value <0.005) in the treatment of moderate to severe ARDS.

CONCLUSION: Our findings suggest that DEXME infusion is beneficial in moderate to severe ARDS caused by SARS-CoV2 when given along with HFNO therapy and prolonged PP sessions, thereby avoiding intubation.

KEYWORDS: Dexmedetomidine, HFNO therapy, PP sessions

Introduction

Since mid-December 2019, the Covid-19 outbreak caused by SARS-CoV2 is one of the worst infectious diseases in history with symptoms ranging from a mild self-limiting disease to a more severe form characterized by acute respiratory distress syndrome (ARDS), septic shock, and even death. [1,2,3] This disease is very contagious and has rapidly spread all over the world. For the treatment of moderate or severe ARDS, both high-flow nasal oxygen (HFNO) therapy and awake prone positioning (PP) had been long established as effective treatments in improving arterial oxygenation and decreasing mortality rates.[4,5,8,9] During the Covid-19 pandemic, research shows that the combined use of HFNO therapy with awake prone position sessions PP can also be used to effectively treat ARDS caused by Covid-19 disease in order to avoid mechanical ventilation. [8,9] However, poor compliance with prolonged sessions of PP limits the use of this technique. Recently, several trials have been successfully conducted to demonstrate the benefits of Dexmedetomidine (DEXME) in Covid-19 patients for the facilitation of long PP sessions. [11,12] DEXME is an alpha-2 agonist which acts on the central nervous system and is an effective anxiolytic, analgesic, and sedative agent. [10,11,12] It has minimum effect on the respiratory drive while decreasing the respiratory rate, thereby improving oxygenation in patients with respiratory failure. [10, 11,,12] It acts rapidly and has cytoprotective and anti-inflammatory properties, both of which can be helpful in the treatment of Covid-19 patients. [10,11,12] This study was conducted to investigate the effectiveness of DEXME as a potent sedative and analgesic agent when used in conjunction with HFNO therapy and long PP sessions for the treatment of moderate to severe pneumonia caused by SARS-CoV2.

Materials and Methods

This is a retrospective cross-sectional observational study that enrolled 150 laboratories tested Real-time RT-PCR positive admitted in Covid ITC, P.A.F Hospital, Mushaf including serving personnel and their dependents, retired and the civilians of all age groups and both genders residing in the premises of PAF Air Base, Mushaf, Sargodha. The time period of this study was 6 months from 1st February 2021 to 31st July 2021. All those patients having mild (PaO2/FiO2 <300), moderate (PaO2/FiO2 <200) or severe (PaO2/FiO2 <100) ARDS were included in the study.

While the following patients were excluded from the study:

1. Patients who tested negative for PCR detection of n-CoV 19.
2. Bacterial pneumonia was found as confirmed by sputum bacterial culture.
3. Patients suffering from interstitial pneumonia have a previous radiological record of their disease.
4. Patients with prior heart failure, associated with pulmonary edema, not caused by Covid-19.
5. Those patients who refused to collaborate with long awake PP sessions or were unable to do it.

Data were collected from patients presenting with high-grade fever, respiratory symptoms such as dyspnea, and shortness of breath along with radiological findings consistent with SARS- CoV2 infection. On HRCT chest scan, the following patients were classified as having mild disease according to W.H.O criteria if they have:

1. Respiratory rate ≤ 30/min during the resting period.
2. Maintaining oxygen saturation (SpO2) ≥ 93% on room air as measured via pulse oximeter.
3. Arterial oxygen partial pressure (PaO2)/oxygen uptake concentration (FiO2) ≥ 300.

While moderate disease was defined as patients having:

1. Respiratory rate ≥ 30/min at resting stage.
2. Maintaining oxygenation level (SpO2) ≤ 93% on room air.
3. Arterial oxygen partial pressure (PaO2)/Fraction of inspired oxygen (FiO2) [PaO2/FiO2] ≤ 300.

Patients were classified as a severe disease with the following characteristics:

1. Flow rate of more than 15L/min for 90% oxygen saturation.
2. HRCT chest scan showing more than 50% involvement.
3. Septic shock leading to multiorgan dysfunction or failure.
4. Blood culture test confirming a secondary bacterial infection.
5. Mean arterial blood pressure raised above 65mmHg by the use of inotropics such as norepinephrine and vasopressor.
6. PaO2/FiO2 ratio less than 100 mmHg.

Patients' oxygen saturation, blood pressure, and heart rate were continuously monitored using a pulse oximeter and a non-invasive blood pressure monitor. Flow rate and FiO2 (50-100%) were titrated to maintain arterial oxygen saturation >90%. Patients were told to remain in the prone position for 2-6 hours during the daytime and more than 6 hours during the nighttime. Continuous intravenous infusion of DEXME was started with a loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2- 0.7mcg/kg/hr when the patients were in the prone position and was titrated to achieve a Richmond Sedation Agitation Scale (RASS) score between 0 and -3. Successful treatment was defined as weaning off of patients from HFNO therapy and their discharge from Covid ITC while the proportion of patients who died while being on HFNO therapy or got intubated was defined as treatment failure. As per protocol, all those who showed impending respiratory failure (respiratory rate >35 and the usage of accessory muscles), unstable hemodynamic status, fatigued, and lethargy were intubated after taking informed consent. The following data were collected: patient's age, gender, comorbidities, PaO2/FiO2 ratio, degree of HRCT involvement, use of HFNO therapy, number of PP sessions and their duration, use of DEXME infusion and its side effects, the need for mechanical ventilation and general ITC outcome.

Data was collected after getting consent from the ethical review committee. (Reference number MSF (H)/308/3/1/Trg dated 25 June 2021) Data were analyzed using SPSS software version 22. Frequencies were calculated along with mean and standard deviation. The Chi-square test was applied to the data. P value <0.005 was considered statistically significant.

Results

Out of these 150 patients who got tested Real-time RT-PCR positive for Covid-19, most (87.5%) of the patients were of the middle age group (50-70 years) of whom 113 (75.3%) were males and 37 (24.7%) were females. Majority of the subjects had comorbidities such as Diabetes Mellitus (67%) and Hypertension (33%). Mild ARDS was observed in 20% (n= 30) of subjects while 69 (46%) patients had moderate ARDS and 51 (34%) patients had severe ARDS. See Figure 1. Only moderate and severe category RDS patients were further studied in the study. These 120 (80%) out of 150 patients were treated with HFNO, DEXME infusion, and long periods of prone position PP sessions. See Figure 2. Among these 120 patients, 90 (75%) were discharged while 30 (25%) patients died out of which 5 (16.7%) died while being on HFNO therapy and 25 (83.3%) patients were mechanically intubated. See Figure 3. DEXME infusion was found to have a positive outcome (P-value <0.005) in the treatment of moderate or severe Covid-19 patients when given in conjunction with HFNO therapy and PP sessions. See Table I and II. Bradycardia was observed as a side effect in 6 (5%) patients during DEXME infusion.

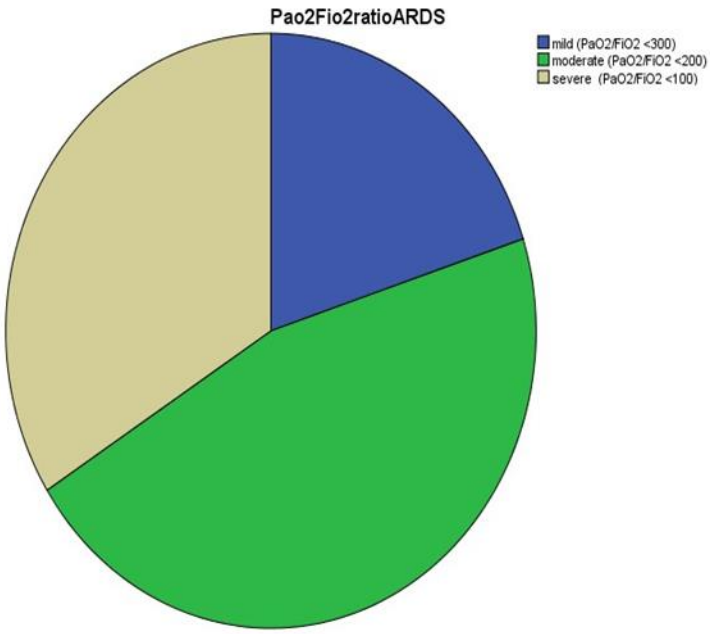

Figure 1: Patients with <300 PaO2/FiO2 ratio had mild disease, Patients with <200 PaO2/FiO2 ratio had moderate disease, Patients with <100 PaO2/FiO2 ratio had severe disease.

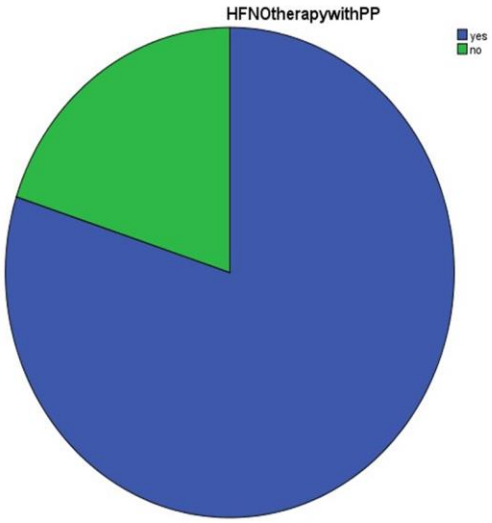

Figure 2: 120 out of 150 patients were treated with HFNO therapy along with long prone position sessions and Dexmedetomidine infusion.

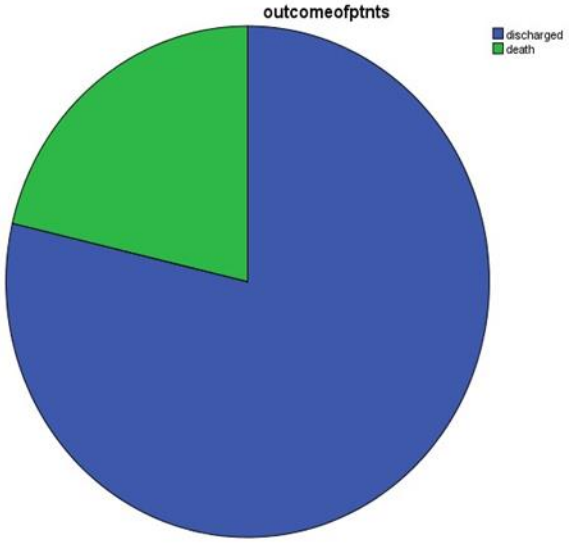

Figure 3: 90/120 patients were discharged while 30/150 died due to disease.

Table I

*HFNOtherapywithPP * outcome of patients Crosstabulation*

			outcomeofptnts		
			discharged	death	Total
HFNOtherapywithPP	yes	Count	90	30	120
		Expected Count	96.0	24.0	120.0
	no	Count	30	0	30
		Expected Count	24.0	6.0	30.0
Total		Count	120	30	150
		Expected Count	120.0 (80%)	30.0 (20%)	150.0

Table II

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.375[a]	1	.002		
Continuity Correction[b]	7.878	1	.005		
Likelihood Ratio	15.160	1	.000		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	9.313	1	.002		
N of Valid Cases	150				

0 cells (0.0%) have an expected count of less than 5. The minimum expected count is 6.00.

b. Computed only for a 2x2 table.

Discussion

Awake-prone positioning has been long established to be effective in the treatment of refractory hypoxia. However, studies conducted during the Covid-19 pandemic proved that long prone position sessions are equally effective in the treatment of pneumonia caused by SARS-CoV 2. [8,9,11,12] One such study was conducted in the University Hospital of Santiago by Taboada M. et al which noted that the oxygenation level of all seven severe Covid ARDS patients improved after each of the 16 PP sessions. [9] Thus, a sedative agent must be added to the treatment to calm the patient for better results and increased patient compliance.

Sedation engages an important role in ICU treatment by reducing pain, anxiety, and agitation, all of which are major issues for patients. Dexmedetomidine is a centrally acting alpha-2 receptor agonist that acts as an anxiolytic and analgesic drug without causing respiratory depression.[13,14,15] Dexmedetomidine may be used successfully to assist with compliance and tolerance, leading to improved oxygen levels and discharge from the ICU without oxygen requirements, in patients who require additional oxygen supplementation in the absence of the necessity of mechanical intubation or who are unable to tolerate HFNO therapy, experience anxiety associated with dyspnea, or who are unable to collaborate with long sessions of awake PP. [13,14,15] Because of its sedative impact, DEXME infusion aids in arousable sedation, which improves compliance to non-invasive ventilation CPAP/ BIPAP in COVID-19 patients.[13,14,15] It also has anti-delirium and opioid-benzodiazepine-sparing potential. [16] According to a review of the literature, DEXME can increase pulmonary hypoxic vasoconstriction, decreasing ventilation/perfusion

mismatch and, as a result, improving oxygen levels. (13,14,15)

Furthermore, it has been shown by previous research that local and systemic inflammatory responses, frequently caused by organ ischemia-reperfusion injury, which is common in septic patients, can in turn trigger irreversible organ damage. These inflammatory responses can be regulated by the cholinergic anti-inflammatory pathway, the key components of which are vagus nerve and nicotinic acetylcholine receptors. Dexmedetomidine has been proven to increase acetylcholine (Ach) release and decrease catecholamine (CA) release, thereby, decreasing inflammation.(18) DEXME can also reduce rI/RI via direct action on alpha 2-adrenergic receptors in renal tubular cells as shown in the study by Gu J. et al (17) Sun Y. et al proved in their study that DEXME can also significantly inhibit LPS-induced histone release, which promotes caspase-1 immunoreactivity in astrocytes and increases the release of pro-inflammatory cytokines such as IL-1β and IL-18 resulting in neuron injury, as well as reduce astrocyte pyroptosis, thereby, possessing neuroprotective effects against acute brain injury in septic patients. (16) All of these studies indicate that DEXME has an anti-inflammatory effect and, therefore, can help reduce the systemic inflammation caused by Covid-19 disease, which can prove to be an important therapy in preventing multi-organ dysfunction and end-organ failure in these patients.

In this retrospective observational study, we found that DEXME along with HFNO therapy and prolonged PP sessions showed a satisfactory outcome of Covid-19 patients who were suffering from moderate to severe ARDS. Our study is consistent with the findings documented in the study conducted by Zhao et al. who also proposed an anti-inflammatory and cytoprotective role of Dexmedetomidine in alleviating COVID-19 cytokine storm-related organ dysfunction based on preclinical research. (13) According to the best of our knowledge, no such detailed study has been conducted nationally on this topic.

Conclusion

Our results indicate that DEXME infusion is beneficial in moderate to severe ARDS caused by Covid-19 when given along with HFNO therapy and prolonged PP sessions thereby, avoiding intubation.

Limitations: This study was conducted in a single center with a small sample size; therefore, more exploratory studies are necessary to apply these relationships in clinical practice.

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