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Dexmedetomidine sedation reduces the incidence of atrial fibrillation in mechanically ventilated patients with COVID-19 pneumonia: A randomized controlled trial

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ABSTRACT

Background: Atrial fibrillation (AF) is a cardiac complication commonly associated with COVID-19 infection, especially in severe cases. The sedative agent dexmedetomidine is known to cause bradycardia. In this study, we are testing whether dexmedetomidine could reduce the occurrence of AF in mechanically ventilated COVID-19 patients.

Methods: This prospective trial included 144 patients who were randomly allocated to one of two groups: Group C patients were sedated with propofol and fentanyl. Group D patients were sedated with the same medications in addition to dexmedetomidine infusion.

Results: Demographic, clinical, and cardiac characteristics of all patients did not significantly differ between the two groups. The duration of intensive care unit (ICU) stay was comparable between the two groups. However, both propofol and fentanyl consumption significantly declined in Group D. The number of AF attacks showed a significant decline in association with dexmedetomidine administration (mean = 12.5% in Group D vs. 29.2% in Group C). Dexmedetomidine also reduced the amount of required electrical cardioversion episodes. Additionally, antiarrhythmic medication needed reduced significantly in Group D. Mortality rates did not differ between the two study groups (58.3% and 63.8% in Groups D and C, respectively).

Conclusions: Dexmedetomidine is associated with a significant reduction in the burden of AF in patients with severe COVID-19 infection, manifested by fewer AF attacks, the need for electrical cardioversion shocks, and the consumption of antiarrhythmic medication without impact on mortality.

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1. Introduction

Covid-19 infection, caused by severe acute respiratory syndrome coronavirus, which emerged in 2019, has had catastrophic global demographic and economic consequences, with approximately six million deaths worldwide by the end of March 2022 [1]. Epidemiological studies of hospitalized patients infected with COVID-19 suggest an elevated risk of atrial fibrillation (AF) in such patients [2,3]. The incidence of this condition in COVID-19 patients ranges between 19% and 21% [4,5], and the risk of arrhythmia flares with high disease severity, particularly in patients requiring admission to the intensive care unit (ICU) [6].

Multiple pathways are incorporated in the pathogenesis of AF in patients infected with Covid-19, including angiotensin-converting enzyme inhibitor 2 downregulation, associated cytokine storm, endothelial dysfunction, hypoxia, fluid and electrolyte imbalance, sympathetic overactivation, and interaction between CD-147 and sialic acid spike proteins [7,8]. This cardiac complication would have a negative impact on the course of this dreadful infectious disease, as it lengthens hospitalization, raises the risk of stroke, and increases mortality [4,9]. Therefore, it is crucial to seek effective medical care methods to improve control and reduce the impact of this cardiac complication [8].

Dexmedetomidine is a sedative, analgesic and anxiolytic that works by activating central alpha-2 adrenergic receptors [10]. Dexmedetomidine is not only considered an effective sedative agent in ICU settings, but it is also associated with shorter ventilation periods, better cognitive outcomes, and shorter ICU stays when compared to other sedative medications [11–13].

Because bradyarrhythmia is a common side effect of dexmedetomidine, it could be utilized to control refractory tachyarrhythmia in both COVID-19 and non-Covid-19 patients [14]. It is yet unknown whether dexmedetomidine can be used to prevent AF [15]. Nonetheless, multiple studies have reported its

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beneficial role in reducing the incidence of atrial tachyarrhythmia following cardiac surgery [16,17].

The present literature lacks clinical trials that address the benefits of this medication in managing AF in COVID-19 patients. Hence, we conducted this study to evaluate whether adding dexmedetomidine to standard sedative agents (propofol and fentanyl) would reduce the incidence of AF in mechanically ventilated patients with COVID-19 pneumonia.

2. Materials and methods

This prospective randomized trial was conducted at Tanta University's Anesthesiology and Intensive Care Department following approval from our medical school's local scientific committee (IRB code: 35028/11/21). The study was conducted over a six-month period, from December 2020 to June 2021. This trial was designed for adult patients were confirmed to have COVID-19 pneumonia (based on clinical, radiological, and nasopharyngeal swab PCR findings), who needed invasive mechanical ventilation, and had established rapid AF. We did not include COVID-19 patients who were under the age of 18 or did not require invasive ventilation and patients with history of chronic AF.

Our sample size was estimated using the SPSS software. We used data previously published by Inciardi and his associates [4] who reported a 19% prevalence of AF in COVID-19 patients. Based on this percentage, 144 patients (72 in each group) were required to detect a 9% difference between the propofol-fentanyl group and the combined dexmedetomidine and propofol-fentanyl group when α and β were 0.05 and 0.2, respectively.

Before enrollment in the study, the patients' first-degree relatives signed informed consent after being told the benefits and possible drawbacks of each approach. A proper patient evaluation was performed in both groups, including history taking and a full clinical and chest examination. Laboratory tests included complete blood count, coagulation profile, serum creatinine, electrolytes, and troponin I. Radiological workup included chest X-ray and computed tomography (if required). These laboratory and radiological investigations were repeated daily for patient monitoring. In addition, analysis of arterial blood gases was performed four times per day. Additional investigations were requested based on the patient's condition and encountered complications.

All patients were started on invasive mechanical ventilation with the following criteria: pressure-controlled ventilation mode (PCV), positive end-expiratory pressure (PEEP) greater than 10 cm.H_2O, adjusted inspiratory pressure (Pi) maintaining a plateau<30 cm.H_2O, and a respiratory rate between 20 and 35 breaths per minute, maintaining the pH above 7.15.

The included patients were randomly assigned to one of two groups (72 in each). Group C included patients who were sedated with propofol infusion (50–200 mg/h) in addition to fentanyl (25–250 mcg/h). Group D included the remaining patients who were sedated with the same medications in addition to dexmedetomidine infusion (0.2–1 mcg/kg/hour). The randomization was done using the sealed envelope method, and the infusion rate in both groups was mostly determined by the patients' hemodynamics.

The incidence of AF during mechanical ventilation was noticed and recorded. A standard 12-lead electrocardiogram (ECG) recording or a single-lead ECG tracing of ≥ 30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF [18]. Ventricular rate (more than 100 bpm) is considered rapid AF. If the patient developed AF, serum troponin and electrocardiography were requested serially throughout the day of an AF episode.

We used electrical cardioversion on patients with rapid AF and hemodynamic instability, with the pads placed over the right sternal border infraclavicular and lateral chest wall. If the patient was able to be moved, the pads were placed over the sternum and between the scapulae. A biphasic defibrillator adjusted to 120–200 joules, synchronized was used to deliver the shocks [19].

In stable patients, IV amiodarone infusion was commenced with a loading dose of 300 mg infused over one hour, followed by a maintenance dose of 900 mg infused over 24 hours with strict monitoring of the blood pressure. Metoprolol tablets (25–50 mg) were also administered twice daily in the nasogastric tube. Moreover, therapeutic anticoagulation was started.

The incidence of AF within 30 days of initiating invasive mechanical ventilation was our primary objective, whereas secondary objectives included the frequency of electrical cardioversion episodes, amiodarone, a metoprolol consumption, and 90-day mortality rates. Patients who died within the 30 days were not included in the study.

The collected data were tabulated and analyzed using the SPSS software. Categorical data were expressed as numbers and percentages, and the Chi-Square test (or Fischer exact test) was used to compare between the two groups. The numerical data was expressed as mean and standard deviation, and the Student t-test was used to compare between the two groups. A *P* value less than 0.05 was considered statistically significant.

3. Results

The demographic characteristics of the included population were as follows. The mean age was 56.17 years in

Table 1. Demographic characteristics and medical history of the study groups.

		Group D ($n = 72$)	Group C ($n = 72$)	95% CI	P
Age (years)		56.17 ± 10.864	54.85 ± 12.880	−2.6, 5.2	0.507
Gender	Male	36.1% (26)	51.4% (37)	−0.01, 0.31	0.065
	Female	63.9% (46)	48.6% (35)		
DM		34.7% (25)	41.7% (30)	−0.1, 0.2	0.391
Arterial hypertension		26.4% (19)	37.5% (27)	−0.04, 0.3	0.153
Mitral regurgitation		5.6% (4)	2.8% (2)	−0.1, 0.04	0.404
Aortic stenosis		4.2% (3)	2.8% (2)	−0.1, 0.05	0.649

Note: Data are presented as mean ± SD, % (frequency). DM: Diabetes mellitus.

Table 2. Incidence of AF of the study groups.

	Study group ($n = 72$)	Control group ($n = 72$)	Odds ratio	P
Incidence of AF	(12.5%) 9	(29.2%) 21	2.88	0.014*

Note: Data are presented as % (frequency), *: Significant P value<0.05. AF: Atrial fibrillation.

Group D and 54.85 years in Group C. Men formed 36.1% of the study participants in Groups D and 51.4% in Group C. All the remaining participants were women. Through their medical histories, it was found that 34.7% and 41.7% of patients in Groups D and C, respectively, had diabetes mellitus, whereas hypertension was prevalent in 26.4% and 37.5% of patients. All these demographic and clinical characteristics, as well as the prevalence of valvular pathologies (regurgitation and stenosis), showed no significant difference between the two groups (Table 1).

As shown in Table 2, there was a significant decline in the incidence of AF in Group D (12.5% vs. 29.2% in controls – p = 0.014).

The mean duration of ICU stay in Group D was 34.47 days versus 32.9 days in Group C, with no statistically significant difference. Nonetheless, both propofol and fentanyl consumption significantly declined in Group D ($P < 0.001$). The average consumption of propofol in Groups D and C was 104.44 and 152.36 mg/hour, respectively, while the average consumption of fentanyl 58.89 and 93.33 mcg/hour (Table 3).

The number of AF attacks significantly declined with dexmedetomidine administration (mean = 6.78 in Group D vs 12.29 in Group C). Furthermore, the mean number of required electrical cardioversion shocks was 2.78 and 4.38 in Groups D and C, respectively, with a significant decrease in group D (Table 4).

In Group D, the total commenced dose of amiodarone and metoprolol was significantly low. The mean values of the first drug dose were 8.56 and 12.24 gm in Groups D and C, respectively, while the mean values of the second dose were 408.33 and 877.38 mg (Table 4).

Forty-two patients died in Group D (58.3%) compared to 46 patients in Group C (63.8%), which was statistically insignificant when comparing the two groups ($P = 0.494$) (Table 5).

4. Discussion

This is the first randomized trial to evaluate the effect of dexmedetomidine in reducing the impact of AF in mechanically ventilated patients with COVID-19

Table 3. Duration of ICU stay and average hourly sedation consumption in the study groups.

	Study group ($n = 72$)	Control group ($n = 72$)	95% CI	P
Duration of ICU stay	34.47 ± 9.197	32.90 ± 10.288	−1.6, 4.8	0.336
Average propofol consumption (mg/h)	104.44 ± 26.690	152.36 ± 28.851	−57.1, − 38.8	< 0.001*
Average fentanyl consumption (mcg/h)	58.89 ± 14.970	93.33 ± 10.615	−38.7, −30.2	< 0.001*

Note: Data are presented as mean ± SD, *: Significant P value<0.05. ICU: Intensive care unit.

Table 4. Characteristics of AF attacks and required treatment in the study groups.

	Group D ($n = 72$)	Group C ($n = 72$)	95% CI	P
Attacks of AF	6.78 ± 1.563	12.29 ± 2.171	−7.2, −3.9	< 0.001*
Electrical cardioversion shocks	2.78 ± 1.093	4.38 ± 0.805	−2.3, −0.9	0.001*
The total dose of Amiodarone (gm)	8.56 ± 0.982	12.24 ± 1.972	−5.1, −2.3	< 0.001*
The total dose of Metoprolol (mg)	408.33 ± 75.000	877.38 ± 162.578	− 585, − 352	< 0.001*

Note: Data are presented as mean ± SD, *: Significant P value<0.05. AF: Atrial fibrillation.

Table 5. Incidence of mortality in the study groups.

	Study group ($n = 72$)	Control group ($n = 72$)	Odds ratio	P
Mortality	58.3% (42)	63.8% (46)	1.264	0.494

Note: Data are presented as % (frequency).

pneumonia. Our study was randomized, as evidenced by the statistically comparable demographic and clinical characteristics of the participants in the two groups. This should also eliminate any bias that might be skewing our findings in favor of one group over the other.

Our findings showed that dexmedetomidine administration reduced propofol and fentanyl consumption, which could be attributed to its sedative effects. These sedative effects are thought to be mediated through activation of pre- and post-synaptic alpha-2 receptors located in the locus coeruleus. It also enhances the endogenous sleep-promoting pathways [20,21].

An important advantage of dexmedetomidine-induced sedation is that it preserves some degree of patient arousability and responsiveness (cooperative sedation) [10]. This advantage, combined with its minimal impact on respiratory drive, makes this drug an optimum choice for sedating patients with respiratory failure in the ICU [22].

Regarding the effects of dexmedetomidine administration on AF outcomes, it was evident that it has a significant beneficial impact manifested by decreased AF episodes, required electrical cardioversion shocks, and antiarrhythmic consumption. Our findings are consistent with previous studies that documented the protective effects of dexmedetomidine in decreasing the incidence of supraventricular arrhythmias [23,24].

In the current study, the incidence of new-onset AF was 20.83% (30 out of 144 cases). One should consider that all of our participants were critically ill patients, and it was previously published that the risk of AF is markedly increased in such patients, including patients with severe pneumonia or acute respiratory distress syndrome [25–27], and the incidence can increase up to 46% according to a previous report [27]. A recent study reported an incidence near ours, as the same complication was encountered in 14.6% of COVID-19 patients, and that study included 109 patients with severe disease requiring ICU admission [28]. Another study reported a 14.9% incidence rate for the included critically ill COVID-19 patients [29].

In contrast to the previous findings, other studies reported a lower incidence of the same cardiac complication in association with COVID-19 infection. Slipczuk et al. reported a 4.22% incidence rate, while Rosenblatt et al. reported a 5.4% incidence rate. It is important to mention that not all the participants of both previous studies had a severe disease or required ICU admission and mechanical ventilation. That may explain the differences in the incidence between studies.

Multiple mechanisms could explain these beneficial effects. These include improved cardiac perfusion, decreased ischemic-reperfusion injury [30,31], decreased cardiac inflammatory response [32,33], and inhibited central sympathetic outflow [34], which is implicated in AF pathogenesis [35]. As stated in the "Introduction" section, all these mechanisms have been implicated in the pathogenesis of AF in COVID-19 patients. Combating them shall have a positive impact on such cardiac problems.

We found only one study evaluating the administration of this medication in a COVID-19 patient with AF. Talib and Ahmed emphasized the beneficial impact of dexmedetomidine in the management of AF in COVID-19 patients. Their case report described a 62-year-old woman diagnosed with COVID-19 infection and having permanent AF with a rapid ventricular response (RVR). Sedation was commenced using fentanyl. Her AF and RVR were refractory to calcium channel blockers (diltiazem), beta-blockers (metoprolol and esmolol), and digoxin load. After shifting her sedation protocol to dexmedetomidine, the authors noticed a significant improvement in her cardiac status one hour after starting the infusion. Her RVR dropped from 140s to 80s. After discontinuing sedation and mechanical ventilation, the patient was discharged and prescribed oral calcium channel blockers, with good monitoring of her AF status. The authors suggested that bradycardia, induced by dexmedetomidine, could be used to control tachyarrhythmias in critically ill patients admitted to the ICU [14]. Our findings are supported by this report.

Our findings showed that dexmedetomidine administration had no significant impact on patient mortality, which was 58.3% and 63.8% in Groups D and C, respectively. This is consistent with the high mortality rates reported in previous studies, which ranged from 71% to 97% [36–40].

Limitations: Although our study has addressed a novel clinical perspective, it has some limitations. The main limitation is the relatively small sample size collected from a single medical center. More studies with larger populations may be needed, particularly to determine whether dexmedetomidine affects mortality in such cases.

5. Conclusion

Based on our findings, it is evident that dexmedetomidine is associated with a significant decrease in the burden of AF in patients with severe COVID-19 pneumonia, manifested by a reduction in AF attacks, applied electrical cardioversion shocks, and antiarrhythmic medication consumption, with no effect on mortality.

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No potential conflict of interest was reported by the author(s).

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