Egyptian Journal of Anaesthesia

Vol. 41, 2025
ISSN: 1110-1849 (print))
ISSN: 1687-1804 (online)
DOI: 10.21608/EGJA.2025.371482.1042

ORIGINAL ARTICLE

Dexmedetomidine Effect on Agitated Psychotic Patients Suffer COPD: A Case Control Study

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Background Mood disorders, neurodegenerative diseases, psychotic disorders, and other mental health issues can cause acute agitation. In extreme cases of agitation, dexmedetomidine might be an effective rescue medication. This work aimed to assess the effectiveness of dexmedetomidine in managing agitation among psychotic patients with severe, acute exacerbations of chronic obstructive pulmonary disease (COPD) caused by chest infections and necessitating non-invasive ventilation (NIV).

Patients and Methods This case-control study involved 70 patients aged >35 years old, both sexes, came to an intensive care unit with exacerbated COPD patients and suffered delirium and agitation. Patients were divided into two equal groups: Group I (control group): non-psychotic cases and Group II (case group): psychotic cases (schizophrenia and bipolar disorders) on medical treatment.

Results There was a significant increase in the failure rate of weaning off NIV in group II than in group I (P<0.001). Regarding Richmond agitation score, patients were more sedated in group I than group II (P= 0.015). Group I had a significant decrease in the effective doses of dexmedetomidine to control agitation than Group II (P<0.001).

Conclusions Dexmedetomidine is the drug of choice to control agitation due to hypoxia and hypercarbia in patients with exaggerated COPD, while it had limited effect on psychotic patients who were on antipsychotic drugs and suffered exaggerated COPD, and this may be due the degree of agitation was severe due to combined factors; the disease of psychosis itself and the effect of hypoxia and hypercarbia.

Keywords Agitation, Chronic Obstructive Pulmonary Disease, Dexmedetomidine, Efficacy, Non-Invasive Ventilation.
Egyptian Journal of Anaesthesia 2025,

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is principally caused by prolonged exposure to hazardous aerosol substances, such as cigarette smoke, and is distinguished by progressive airway obstruction and lung tissue injury. This exposure induces structural alterations and chronic inflammation, resulting in airway narrowing and reduced lung elasticity [1]. Increased airway inflammation, increased mucus production, and gas trapping are the hallmarks of a COPD acute exacerbation [2]. These episodes can vary in severity, ranging from self-limiting conditions to severe hypercapnic respiratory failure that necessitates non-invasive ventilation (NIV) and late may be mixed type of respiratory failure due to hypercarbia and hypoxia and patients may need ventilation [3].

In a patient with COPD experiencing distress and hypoxemia, non-compliance with the NIV mask can hinder the necessary ventilatory support required to improve oxygenation. When NIV with a tight-fitting

mask fails to achieve the desired outcomes, emergent endotracheal intubation may be necessary to prevent severe complications such as profound hypoxemia and subsequent cardiac arrest [4].

Agitation is a medical condition that needs medical treatment right away because it causes aggressive actions, impatience, anxiety, and excessive activity or speaking without a clear goal [5].

A wide variety of psychological and behavioral abnormalities may be characterized as psychiatric diseases; these disorders cause substantial suffering and functional impairment due to their origins in underlying psychobiological dysfunction. Patients who already have a mental health condition are more likely to have negative health consequences when they are in the intensive care unit (ICU) [6].

Dexmedetomidine has sedative, hypnotic, and anxiolytic effects via its action on α2-adrenergic receptors, however it does not cause substantial respiratory depression [7]. In addition to these effects, the medication may facilitate natural sleep by stimulating α2- receptors, leading to decreased noradrenergic signaling in the locus ceruleus and increased GABAergic signaling in the ventrolateral preoptic nucleus [8].

This work aimed to assess the effectiveness of dexmedetomidine in managing agitation among psychotic patients with severe, acute exacerbations of COPD caused by chest infections and necessitating NIV.

PATIENTS AND METHODS

This case-control study involved 70 patients aged >30 years old, both sexes, came to ICU with exaggerated COPD and suffered delirium and agitation. All of the patients were smokers. Following approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt (36264PR678/5/24) and registration of clinicaltrials.gov (ID: NCT06567587), the research was conducted from June 2024 to December 2024. An informed written consent was obtained from the patient or relatives of the patients.

Exclusion criteria were mild and moderate degree of severity of exacerbation of COPD, patients with GCS <8 (need invasive ventilation), hemodynamic instability, invasive mechanical ventilation, fascial trauma or surgery, esophageal varices and recent GIT surgeries.

Patients were divided into two equal groups: Group I (control group): non-psychotic cases and group II (case group): psychotic cases (schizophrenia and bipolar disorders) on medical treatment (Risperidone 2mg OD).

Glasgow Coma Scale (GCS) of the patients was evaluated, inspection of the chest expansion, pattern of breath and measure respiratory rate, then percussion of the chest to know if there may be pneumothorax or chest consolidation and auscultation of wheeze or crepitation all these were done with evaluation for O_2 saturation, respiratory rate, heart rate, blood pressure, and ABG samples were taken to assess CO_2 level and chest x-ray was done. Patients were put on low flow oxygen guided to obtain O_2 saturation between 88-92%, inserted IV line for rehydration and medical treatment was given in the form of bronchodilators, antibiotics and corticosteroids. CO_2 after separation is between 40 and 60 for all cases in both groups. According to degree of agitation, we can control the patients by de-escalation, medication and restraint in severely agitated patients. Sedation was achieved in agitated patients with hypercarbia by starting them on NIV and administering a loading dose of dexmedetomidine at 1μg/kg over 10 minutes, followed by a maintenance dose of 0.2-0.7μg/kg/hr, adjusted according to the patient's weight. Sedation was guided by the RASS, with target scores ranging from -2 to 0. To find the percentage of RASS measurements that were within the target range, we divided the total number of assessments that met the goal by the total number of RASS evaluations that were performed. In accordance with institutional policy, RASS assessments were performed at least every four hours or whenever medication adjustments were made.

Weaning from NIV was planned when patients became fully conscious, calm, and free of dyspnea while receiving inhaled oxygen at a fraction of inspired oxygen of 40% in the Bi-level positive airway pressure mode. Additionally, weaning criteria included achieving a partial pressure of arterial oxygen of at least 100mmHg while breathing room air.

The primary outcome was the failure rate of weaning off NIV within one week. The secondary outcomes were Richmond agitation score and effective doses of dexmedetomidine to control agitation.

Sample Size Calculation

G*Power 3.1.9.2 (Universität Kiel, Germany) was employed to ascertain the sample size. Results of our pilot study on 10 patients in each group showed that 60% of the Control Group and 20% of the Case group needed to transition to invasive ventilation after NIV. The calculation took into account the following parameters: a 95% confidence level, 80% power, a Group allocation ratio of 1:1, and three more cases were added per group to overcome drop out. Consequently, the study will enroll 26 patients in each group.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was employed to conduct statistical analysis. The two groups were compared using an unpaired Student's *t*-test for quantitative data, which were stated as means and standard deviations (SD). When applicable, we used Chi-square or Fisher's exact test to analyze the percentage and frequency of qualitative variables. Statistical significance was determined by a two-tailed *P* value less than 0.05.

RESULTS

Demographic data was insignificantly different between both groups (Table 1).

There was a significant increase in the failure rate of weaning off NIV in group II than in group I [25(71.43%) vs 9(25.71%), *P*<0.001) with a relative risk (95% CI) of 2.6(1.49:4.55) (Figure 1).

Table 1: Demographic data of the studied group:

		Group I (*n*=35)	Group II (*n*=35)	*P*	Mean difference/RR (95%CI)
Age (years)		47.57±8.76	48.51±8.75	0.654	-0.94(-5.12: 3.23)
Sex	Male	2(5.71%)	3(8.57%)	1	0.67(0.12:3.75)
	Female	33(94.29%)	32(91.43%)		
Adjusted body weight (kg)		85.09±16.61	86.46±18.03	0.742	-1.37(-9.64: 6.9)
APATCH scores		19.94±2.21	21.2±4.17	0.120	-1.26(-2.85 :0.33)

Data are presented as mean±SD or frequency (%); RR: Relative risk; CI: Confidence interval.

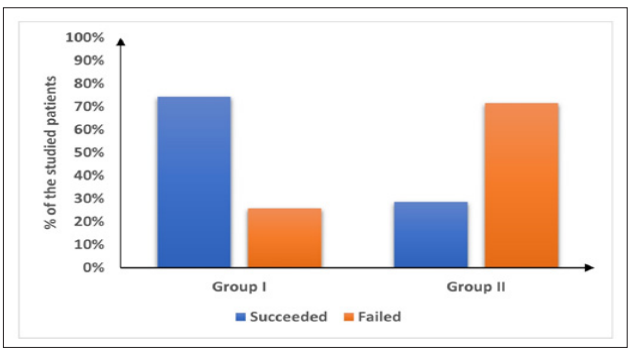

Figure 1: Failure rate of weaning from non-invasive ventilation

Patients in group I were more sedated than group II regarding Richmond agitation score (*P*= 0.015). The effective dosages of dexmedetomidine to reduce agitation were significantly lower in Group I than in Group II (*P* < 0.001) (Table 2).

Heart rate and mean arterial blood pressure were insignificantly different before treatment and were significantly lower in group II than group I (*P*<0.05) after treatment (Table 3).

Table 2: Richmond agitation score and effective doses of dexmedetomidine to control agitation of the studied group:

		Group I (*n*=35)	Group II (*n*=35)	*P*	Mean difference (95%CI)
Richmond agitation score over 48h	>0	9(25.71%)	21 (60%)	0.015*	------
	-2 to 0	21(60%)	11 (31.43%)		
	<-2	5(14.29%)	3 (8.57%)		
Effective dose of dexmedetomidine to control the agitation (µg/kg/h)		0.41±0.21	0.57 ± 0.16	<0.001*	-0.16(-0.25: -0.07)

Data are presented as mean±SD or frequency (%); * Significant as *p* value <0.05; NIV: Non-Invasive Ventilation; CI: confidence interval.

Table 3: Heart rate and mean arterial blood pressure of the studied group:

	Group I (*n*=35)	Group II (*n*=35)	*P*	Mean difference (95%CI)
Heart rate before (beats/min)	97.6±11.34	101.54±12.38	0.169	-3.94(-9.6: 1.72)
Heart rate after (beats/min)	94.09±11.24	86.77±13.27	0.015*	7.31(1.45: 13.18)
Mean arterial blood pressure before (mmHg)	110.6±12.3	108.77±14.69	0.574	1.83(-4.63: 8.29)
Mean arterial blood pressure after (mmHg)	106.91±12.28	97.37±15.86	0.006*	9.54(2.78: 16.31)

Data are presented as mean±SD; *: Significant as *p* value <0.05; CI: Confidence interval.

DISCUSSION

Patients often exhibit psychomotor agitation when seen in medical and mental health facilities. Aggression and violence are possible outcomes of the disorder's symptoms, which include agitation, irritability, anxiety, and excessive or excessive movement. It may show up as a symptom of medical or neurological disorders, substance abuse, decompensated thinking disorders, or mood disorders [9].

Dexmedetomidine has sedative, anxiolytic, hypnotic, and analgesic effects due to its highly selectivity to α2-adrenergic receptor, Consequently, dexmedetomidine reduces the activation of locus coeruleus neurons and inhibits excessive sympathetic activity, making it an effective treatment for acute agitation associated with bipolar disorder or schizophrenia [10].

Most of studies described using of dexmedetomidine by sublingual rout to control acute agitation in psychiatric patients [11], but in our study we used the intravenous route for dexmedetomidine as we used intravenous lines for drugs administration like antibiotics and corticosteroid. We tried to take care of intravenous lines by reducing violent movements by de-escalation, antipsychotic drugs administration and restraints in severely agitation patients.

Excessive administration of dexmedetomidine may lead to side effects such as hypotension, bradycardia, or prolonged sedation, often resulting from drug accumulation in the body, so we adjust the dose of dexmedetomidine according to adjusted body weight, as according to Atyia SA *et al*., [12] discovered that when sedation was administered to critically ill obese patients in the intensive care unit using adjusted body weight rather than actual body weight, there was no statistically significant difference in the percentage of RASS measurements within the target range. The study of Akhtar *et al*., [13] coincided with our study in proving that dexmedetomidine shorten the time of staying patients on NIV. Other study made by Lewis *et al*., [14] verified that compared to other sedative strategies, dexmedetomidine reduces the risk of intubation. On the opposite way Devlin *et al*., [15] confirmed that that beginning dexmedetomidine soon after NIV starts did not improve NIV tolerance or make it easier to maintain the required level of sedation in patients with ARF. The study of Akhtar MH *et al*., [13] coincided with our study in proving that prior to the intervention, the RASS scores of our patients were +2 or +3, indicating moderate agitation. However, after incorporating dexmedetomidine into the treatment protocol, the scores improved to -1 or -2, reflecting a more sedated state. It should be mentioned that the dosage of dexmedetomidine differed in our approach; unlike other protocols, we used a loading dosage of 1mcg/kg was given over 10 to 15 minutes and then adjusted to a range of 0.2 to 0.7mcg/kg/h. Alongside to our study, Kawazoe Y. *et al*., [16] proved that patients administered dexmedetomidine had a much greater incidence of controlled sedation throughout their ICU stay. The exact goals for sedation depth were a RASS score of 0, which signifies a relaxed state during the day, and a RASS score of −2, which indicates mild sedation at other times.

According to the dose we used in our study, it was alongside the study of Obara [17] who administered the same loading and maintenance doses In order to obtain the desired effect, a loading dosage of 1mcg/kg was given over 10 to 15 minutes and then adjusted to a range of 0.2 to 0.7mcg/kg/h. In this study, a comparison was made between BMI, total body weight, and lean body mass as potential guides for determining the appropriate weight based. The study of Akhtar MH. *et al*., [13] employed a bolus dosage of 0.2-0.3 mcg/kg and maintained an infusion of 0.3 to 0.4mcg/kg/hr to decrease the hemodynamic changes occurred with large dose of dexmedetomidine in COVID patients, while in our study we depend on the usual dose but depend on adjusted body weight so there were no hemodynamic changes observed throughout our study.

All studies which used dexmedetomidine to control agitation for psychotic patients used sublingual form of dexmedetomidine as for mild or moderate degrees of agitation they used 120mcg SL initially, if agitation persists, may give 60mcg for up to 2 doses at least 2hr apart; not to exceed 240mcg/day. While in severe form of agitation they gave 180mcg SL initially, if agitation persists, may give 90mcg for up to 2 doses at least 2hr apart; not to exceed 360mcg/day [18].

Pharmacokinetic research has demonstrated that a single sublingual dosage of dexmedetomidine provides an absolute bioavailability of 72% when supplied sublingually [10], compared to 100% bioavailability following intravenous administration which we have employed in our work.

According to Preskorn SH. *et al*., [11], the objective of this research was to determine if at 120µg or 180µg, a single sublingual dose of dexmedetomidine could successfully reduce symptoms of acute agitation. The results demonstrated a significantly greater decrease in agitation scores two hours after administration. Also, Smith CM. *et al*., [10] demonstrated that sublingual dexmedetomidine is the first medicine to have been approved by the FDA in the last ten years for the treatment of acute agitation in people with schizophrenia or bipolar I disorder, and it is also the first medication to have been approved for the treatment of agitation specifically associated with bipolar II disorder. Other studies done by Citrome *et al*., [19] and Karlin *et al*., [20] proved the same result of the effectiveness

of sublingual dexmedetomidine in control agitation in psychotic patients.

Limitations of the study included that the dose of dexmedetomidine used in Group II was not sufficient to control agitation in psychotic patients suffered exaggerated COPD as we feared if we used high doses patients suffered bradycardia and hypotension. We had to restrain patients to avoid self-harm behaviors and despite that intravenous lines had come off and we had to reinsert many lines at beginning.

CONCLUSION

Dexmedetomidine is the drug of choice to control agitation due to hypoxia and hypercarbia in patients with exaggerated COPD, while it had limited effect on psychotic patients who were on antipsychotic drugs and suffered exaggerated COPD, and this may be due the degree of agitation was severe due to combined factors; the disease of psychosis itself and the effect of hypoxia and hypercarbia.

ETHICS APPROVAL AND CONSENT FOR PARTICIPANTS

Following approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt (36264PR678/5/24) and registration of clinicaltrials.gov (ID: NCT06567587), the research was conducted from June 2024 to December 2024. The patients' written informed consent was acquired.

AUTHORS' CONTRIBUTIONS

Study concept and design: M.Z.W., L.A.E. and M.A.A.; analysis and interpretation of data: M.Z.W.; drafting of the manuscript: L.A.E.; critical revision of the manuscript for important intellectual content: M.Z.W., L.A.E. and M.A.A.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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