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Efficacy and safety of medroxyprogesterone acetate on noninvasive ventilation -treated exacerbated COPD patients: a double-blind randomized clinical trial

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Abstract

Background In acute exacerbation periods of chronic obstructive pulmonary disease (COPD), patients may experience hypoxemia or hypercapnia. Noninvasive ventilation (NIV) and respiratory stimulant drugs are used to treat this condition. Medroxyprogesterone acetate (MPA) can cross the blood-brain barrier and cause breathing stimulation and hyperventilation. This study was conducted to investigate the effectiveness of MPA in hypercapnic exacerbated COPD patients and the possibility of faster weaning of patients from NIV.

Materials and methods This double-blind clinical trial was conducted on consecutive exacerbated COD patients referred to Shahid Rahnemoun Hospital, Yazd, Iran, from February 2022 to August 2022. Through a block randomized sampling method with a 1:1 allocation ratio, 58 eligible patients with hypercapnic exacerbated COPD on NIV were divided into two study groups: the intervention (treated with MPA 10 mg every 8 h) and the control (treated with placebo). The clinical and arterial blood gas (ABG) parameters were investigated in both groups.

Results Out of 50 patients, 27 and 23 intervention and control arms cases were analyzed. Although there was a significant difference in the amount of ABG parameters during the study in each group, there was no statistically significant difference between the two groups. Also, There was no significant difference in the total weaning rate of the patients in the two groups. Despite the higher number of early weaning in the MPA group, no significant difference was reported between the two groups in this regard. In addition, there was no difference between the two groups in the rate of ICU hospitalization, the length of stay of hospitalization and ICU, and the mortality rate.

Conclusion The administration of MPA has not improved clinical and laboratory results, and MPA is not superior to placebo in the weaning process of patients undergoing NIV.

Trial registration IRCT20190810044500N21 (01/02/2022), (https//irct.behdasht.gov.ir/user/trial/59402/view)

Keywords COPD, Exacerbation, Hypercapnia, NIV, Medroxyprogesterone acetate, RCT

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Background

COPD is the third cause of death, so in 2019, it was the cause of three million deaths worldwide [1]. This disease is characterized by chronic and irreversible airway obstruction [2, 3]. It is associated with periods of acute exacerbation of the disease, characterized by worsening acute respiratory symptoms in patients. It leads to hospital or Intensive Care Unit (ICU) admission and an increased financial burden on the healthcare system. Patients may experience hypoxemia or hypercapnia in acute exacerbation periods due to gas exchange disorders requiring noninvasive or invasive ventilation in severe cases [4, 5]. According to previous studies, despite existing treatments, the mortality rate of patients with acute exacerbation of COPD admitted to the ICU is still high. Treatments that can improve the results of patients are essential from medical, social, and economic points of view [6, 7]. Respiratory failure in these patients may be due to the decrease in the drive of the respiratory center, the diminished respiratory muscle strength, and the respiratory workload elevation. Therefore, mechanical ventilation and respiratory stimulant drugs are used to treat this condition [5, 7, 8].

NIV is the first line in treating exacerbated COPD patients with hypercapnic respiratory failure [9]. The NIV in exacerbated COPD patients reduces the need for endotracheal intubation and mortality [6, 7, 10–13].

Using respiratory agents was recommended in the treatment of COPD patients with severe disease [14]. Many drugs have the property of respiratory stimulation, but their use is limited due to toxicity in the clinical setting [15]. One of the respiratory stimulating drugs used in these patients is medroxyprogesterone acetate (MPA) [16]. MPA is an oral synthetic progesterone-derived agent. The idea of using progesterone as a respiratory stimulant came from observations related to hyperventilation in pregnant women and their menses period, which is related to the serum level of progesterone [17, 18]. Progesterone is a steroidal hormone that is synthesized in the ovaries by provocation of luteinizing hormone [19]. Although many studies have revealed the relation between respiratory stimulation of MPA and hyperventilation, the precise mechanism of its action remains unclear [20]. Due to its lipophilic properties, MPA can cross the blood-brain barrier and cause breathing stimulation and hyperventilation [21, 22]. It was shown that MPA was able to stimulate respiration in normal persons and patients with respiratory disorders [15]. MPA increased minute ventilation in response to both hypoxia and hypercapnia [23]. Previous studies showed that MPA had increased the oxygen pressure and decreased the carbon dioxide tension in the arterial blood of COPD patients. Skatrud and Dempsey conducted a study comparing the effectiveness of MPA and acetazolamide in COPD patients. According to their findings, both drugs led to increased P0.1, tidal volume, and mean inspiratory flow in eleven out of 15 patients [24]. In a separate study, 20 mg of MPA was administered three times a day to 17 men and two women with COPD. The study's findings indicated that MPA improved oxygenation, reduced PCO2, and increased PH in awake patients. However, it did not significantly impact the patients' sleep disorders and only partially improved oxygenation during sleep [25]. In a study by Daskalopoulou et al., it was demonstrated that the administration of MPA improved the ventilatory response to hypercapnia in COPD patients. This led to a greater reduction in PCO2 compared to treatment with almitrine bismesylate. The study also revealed that MPA reduced hypoxemic episodes during sleep [26].

The best place to initiate NIV therapy is yet to be determined; some believe it should start in the ICU, but this is only sometimes feasible due to the need for additional facilities and ICU beds [13, 27]. Based on our experimental observations at our hospital, we have noticed a shortage of non-invasive ventilation (NIV) devices for patients. Due to this shortage, it is crucial to consider alternative medications that can promote faster recovery and weaning for patients undergoing NIV. Research has shown that in patients experiencing acute exacerbation of COPD, the use of acetazolamide as a respiratory stimulant has led to a reduction in the duration of NIV [28]. Based on our research, no studies have examined the effectiveness of MPA in patients experiencing an acute exacerbation of COPD. Consequently, our study was carried out to assess the effectiveness of MPA in COPD patients experiencing exacerbation and to explore the potential for quicker weaning of patients from NIPPV.

Methods

This double-blind, randomized, controlled clinical trial (RCT) was conducted on patients with exacerbated COPD who were referred to Shahid Rahnemoun Hospital in Yazd, Iran, from February 2022 to August 2022.

Inclusion and exclusion criteria

This study included patients with COPD and hypercapnic respiratory failure. The patients were classified as having COPD based on their clinical characteristics, physical examination, and imaging. The study included patients with moderate, severe, and very severe COPD. The severity of the disease was determined based on the patients' most recent spirometry results from the last 6 months. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the inclusion criteria were a FEV1 to FVC ratio less than 0.7 and FEV1 less than 80% [1, 29]. Hypercapnic respiratory failure is defined as respiratory acidosis (pH below 7.35 and arterial blood gas

analysis showing carbon dioxide tension (PCO2) above 50 mmHg) with or without hypoxemia.

The following groups of patients were excluded from the study: those who were pregnant or lactating, those who had intolerance to non-invasive ventilation (NIV), those with cystic fibrosis or disseminated bronchiectasis, those with Alzheimer's disease, those who had a tracheostomy, those who chronically used respiratory stimulant agents, those who used sedative drugs, those with a history of medroxyprogesterone allergy, those with decompensated heart failure, liver or kidney failure, those who needed immediate admission to the intensive care unit (ICU) for any reason, and those with a history of using NIV at home. Additionally, patients who required endotracheal intubation during the first 24 h of hospitalization were also excluded.

Randomization and blinding

In this RCT, 58 eligible patients were divided into two study groups using a block-randomized sampling method with a block size of 4 and a 1:1 allocation ratio. Randomization of patients started from the first day of hospitalization in the ward. There were 29 cases in the intervention group and 29 cases in the control group. All patients were clinically followed up daily. The treating physician, patients, and the evaluator were unaware of the treatment assignment throughout the study until the clinical database had been locked.

Intervention

Patients in the intervention group were administered 10 mg of medroxyprogesterone acetate tablets (manufactured by Iran Hormone Pharmaceutical Company) every 8 h for 96 h. Meanwhile, patients in the control group were given placebo tablets prepared in the Pharmaceutics Laboratory of Shahid Sadoughi School of Pharmacy, Yazd, Iran. Both groups of patients received routine treatment for COPD exacerbation, which included antibiotic treatment, inhaled bronchodilator and systemic anti-inflammatory agents, oxygen therapy as needed, and NIV. Oronasal masks were used for NIV in all patients. The NIV device settings were adjusted by a single pulmonologist with eight years of experience in the medical ICU. Noninvasive mechanical ventilation was executed using Bilevel positive airway pressure (BIPAP) mode. The initial default setting for starting NIV was EPAP 4 to 6 cm of water and PS 8 to 10 cm of water, which was then adjusted based on arterial blood gas (ABG) levels two hours later and the patient's clinical condition. Patients' treatment was adjusted based on their clinical conditions and arterial blood gas parameters, were measured daily. The nurses caring for the patients had at least six months of experience with NIV. Additionally, all patients were continuously monitored with cardiac and pulse oximetry.

Outcomes

In this study, we collected demographic information such as age, sex, comorbidities, and causes of COPD. We also recorded spirometric indices including Forced Expiratory Volume in 1 s (FEV1) and Forced Vital Capacity (FVC), as well as clinical characteristics of the patients using a pre-designed checklist. The clinical characteristics included arterial blood gas (ABG) parameters (PH, PaCO2, PaO2, and HCO3), Glasgow Coma Scale (GCS) score, duration of NIV use, rate of endotracheal intubation and ICU admission, hospital and ICU length of stay, successful weaning rate, complication and mortality rates. Additionally, we recorded the pressures required for noninvasive ventilation, including primary expiratory positive airway pressure (EPAP) and primary and maximum pressure support (PS). PS is defined as the difference between the Inspiratory Positive Airway Pressure (IPAP) and EPAP.

Successful weaning was defined as meeting the following criteria: requiring a PS level of less than 6 cm H2O, achieving PaCO2 levels less than 45 mmHg, resolving respiratory distress, and the patient being fully conscious. Patients who couldn't tolerate NIV for at least 18 h per day were considered NIV intolerant, identified through nursing reports. Any need for endotracheal intubation and initiation of mechanical ventilation during hospitalization was considered a primary treatment failure.

The main objective of this study was to assess the effectiveness of MPA in discontinuing NIV and its impact on ABG levels. Secondary goals included evaluating the duration of NIV, the necessity of endotracheal intubation and admission to ICU, mortality rates, as well as the length of hospital and ICU stay.

Sample size:

Based on prior experience, we estimated a sample size of 20 per group to detect a significant difference of at least eight units in the average PaCO2 between two groups using the sample size equation.

$n = \frac{(Z_{(1-\frac{\alpha}{2})}+Z_{1-\beta})^2 2S^2}{(\mu_1-\mu_2)^2}$, For comparison of the two means, the estimated sample size was increased to 22 per group to account for potential 10% attrition ($\alpha = 0.05$; $\beta = 0.2$).

Ethics

The healing attempts were in agreement with the Declaration of Helsinki and with local regulations and local regulatory authorities. This study was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.MEDICINE.REC.1400.291), and performed by the CONSORT guidelines and reported the required information. The study was registered with the Iranian Clinical Trial Registry (IRCT20190810044500N21 (01/02/2022), https://irct.b

ehdasht.gov.ir/user/trial/59402/view*)*. All patients gave written informed consent before enrollment into the study.

Statistical analysis

Statistical analysis was performed using SPSS version 26 software. Quantitative and qualitative variables were reported as Mean, SD, and frequency, respectively. Kolmogorov-Smirnov was used to analyze the normality of quantitative variables. An independent t-test was performed to compare between groups, and a paired t-test and repeated measures ANOVA test were performed to compare within groups. In addition, regarding qualitative variables, Chi-square and Fisher's exact tests were used. *P-value* ≤ 0.05 was considered statistically significant.

Results

In this RCT, 27 and 23 patients in the MPA and placebo groups were subjected to statistical analysis. During follow-up, 2 and 6 cases were excluded from the intervention and control groups, respectively (Fig. 1). As Shawn in Table 1, no significant differences were found between the baseline demographic, clinical, and para-clinical parameters.

In the present study, the clinical characteristics of patients were recorded daily. The findings of ABG Parameters three times (at the baseline, at the mid-time

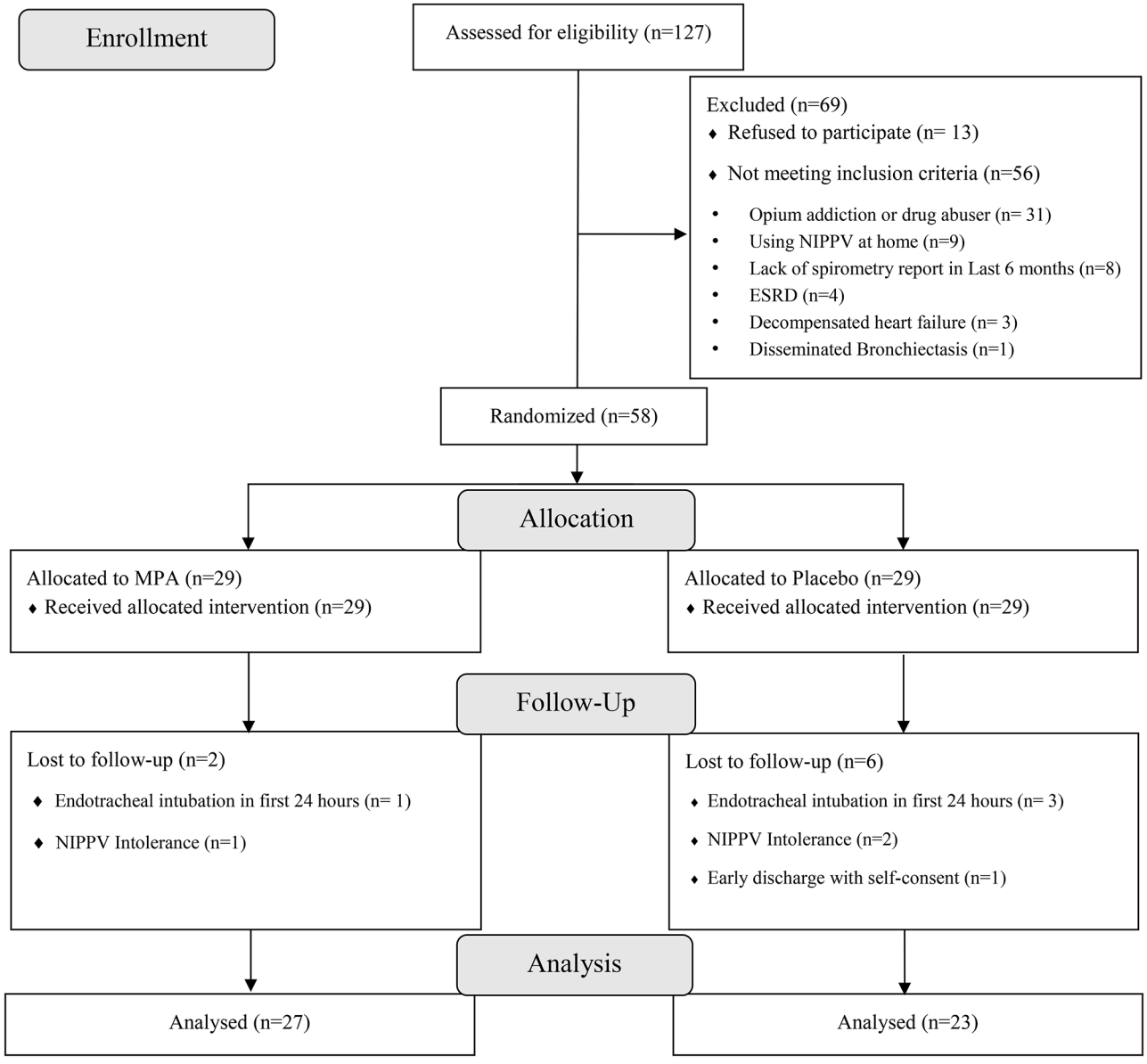

Fig. 1 CONSORT flow diagram

Table 1 Comparison of primary demographic and clinical variables between the two study groups

Primary Variables		MPA ($n=27$)	Placebo ($n=23$)	*P*-Value
Age, y	**Mean ± SD**	64.22 ± 9.03	66.83 ± 12.60	0.40
BMI, kg/m^2		23.67 ± 3.39	24.95 ± 5.57	0.32
FEV1, liters		58.89 ± 13.72	54.83 ± 16.27	0.34
FVC, liters		72.11 ± 9.14	73.26 ± 1.61	0.63
Smoking (Pack-Year)		44.50 ± 21.63	46.00 ± 21.64	0.84
Exacerbation		1.00 ± 1.00	1.35 ± 1.07	0.24
PS		11.30 ± 2.49	11.43 ± 2.59	0.84
EPAP		5.11 ± 2.57	5.04 ± 3.73	0.94
Sex (Male)	**N (%)**	24 (88.9)	20 (86.9)	0.58
COPD Etiology		19 (70.3)	15 (62.5)	0.69
Smoking		6 (22.2)	4 (17.4)	0.47
Occupational		3 (11.1)	3 (13.0)	0.58
Traditional Cooking		1 (3.7)	1 (4.3)	0.71
Idiopathic				
Comorbidities		16 (59.3)	12 (52.2)	0.61
HTN		5 (18.5)	1 (4.3)	0.13
IHD		4 (14.8)	2 (8.3)	0.41
DM		0 (0.0)	2 (8.7)	0.20
CKD				
GOLD Stage		21 (77.8)	16 (69.6)	0.70
2		5 (18.5)	5 (21.7)	
3		1 (3.7)	2 (8.7)	
4				

N: Number; SD: Standard Deviation; %: Percent; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; MPA: Medroxyprogesterone Acetate; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in second 1; GCS: Glasgow Coma Scale; EPAP: Expiratory Positive Airway Pressure; PS: Pressure Support; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FVC: Forced Vital Capacity; y: year; kg/m^2: Kilograms per Square Meter

Table 2 Comparison of ABG parameters in the three periods between the two studied groups

Variable		MPA ($n=27$)	Placebo ($n=23$)	*P*-Value[a]
		(Mean ± SD)		
PH	Start	7.28 ± 0.07	7.32 ± 0.05	0.07
	Mid	7.32 ± 0.08	7.35 ± 0.07	0.18
	End	7.37 ± 0.10	7.39 ± 0.04	0.54
Within groupP-Value[b]		0.001	0.001	
PCO2	Start	72.22 ± 13.98	64.92 ± 12.18	0.57
	Mid	61.27 ± 14.13	57.38 ± 11.12	0.29
	End	50.14 ± 12.19	52.36 ± 7.38	0.45
Within groupP-Value[b]		< 0.0001	0.001	
PO2	Start	38.83 ± 15.79	45.96 ± 16.89	0.13
	Mid	47.29 ± 24.84	45.01 ± 17.14	0.71
	End	50.08 ± 26.97	52.87 ± 17.94	0.67
Within groupP-Value[b]		0.181	0.312	
HCO3	Start	33.89 ± 7.06	33.15 ± 4.29	0.66
	Mid	30.33 ± 5.87	32.36 ± 4.73	0.19
	End	29.41 ± 4.30	32.03 ± 3.65	0.02
Within groupP-Value[b]		0.015	0.655	

[a] Student's t-test; [b] Repeated Measures ANOVA

of the intervention (48 h after the start of the study), and at the end of the intervention (96 h after the start of the study)) were analyzed with repeated measures ANOVA. Although there was a significant difference in the amount of ABG parameters in each group during the study, there was no statistically significant difference between the two groups with Student's t-test (Table 2). Figure 2 shows the mean difference of ABG parameters at three different time points of the study.

In terms of the Clinical outcome of the patients, no significant difference was seen between the two groups. The total weaning rate of patients in the MPA and placebo

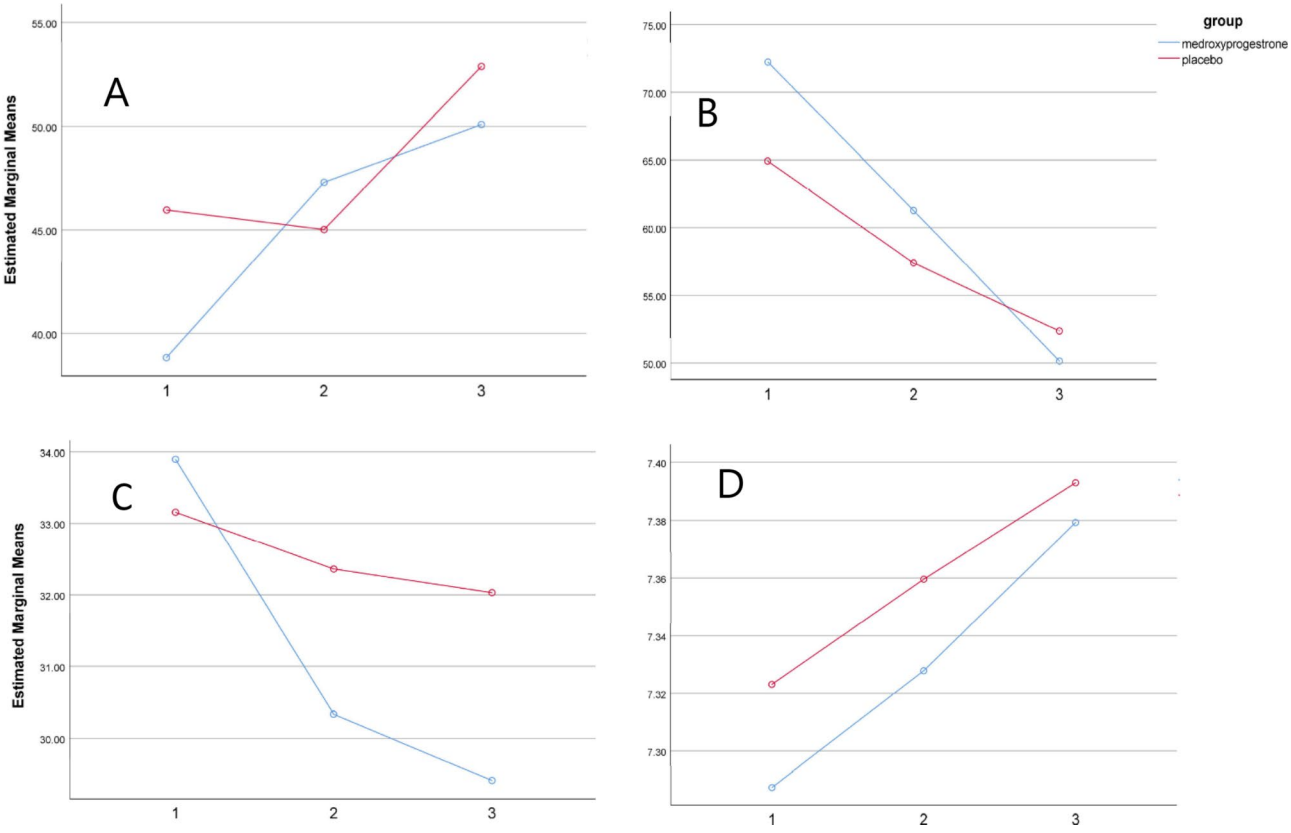

Fig. 2 Mean Differences of ABG parameters (**A**: PH; **B**: $PaCO_2$; **C**: PaO_2; **D**: HCO_3) between study Groups at different Time Points; (1: Start of the intervention; 2: Mid time of the intervention; 3: End of the intervention)

groups was 11 and 9, respectively (*P-Value* = 0.23). Out of the 11 cases of weaning in the MPA group, three cases were on the first four days, and the weaning time in 8 cases was after the fourth day of hospitalization. In the placebo group, all nine weaning cases were after the fourth day of hospitalization. However, there was no significant difference between the two groups (*P-Value* = 0.145). During the study, 17 patients (including 10 patients in the MPA group and seven patients in the placebo group) needed to be admitted to the ICU due to the deterioration of their clinical condition (*P-value* = 0.42). The cause of hospitalization in 6 cases (60%) in the MPA group and five cases (71.4%) in the placebo group were due to pulmonary causes, and the remaining cases were due to non-pulmonary causes. Other study findings showed that the maximum of PS required ventilating to MPA and placebo groups were 16.93 ± 3.82 and 17.17 ± 3.35, respectively, and was not statistically significant (*P-Value* = 0.21) (Table 3). No adverse effects were seen in any of the participants who completed the treatment period.

Discussion

Various studies have investigated the use of respiratory stimulating drugs in weaning from the ventilator [10, 30, 31]. However, limited studies have been conducted on using these drugs in weaning from NIV [28]. According to our findings, the current study is the first to investigate the effectiveness and safety of MPA in the weaning of Exacerbated COPD patients with hypercapnia treated with NIV.

The current study showed that MPA is not superior to placebo in the weaning process of patients undergoing NIV. The administration of MPA has not improved clinical and laboratory results in Exacerbated COPD patients. Fontana et al. showed that acetazolamide improves the clinical condition and blood gas parameters in patients with COPD exacerbated by metabolic alkalosis treated with NIV [28]. Despite the positive results of their study, the number of participants in the RCT was small, and acetazolamide was administered in only two days. Compared to Fontan's study, our study was conducted with a larger sample size and a longer duration of medication. Still, positive clinical and laboratory results were not observed in the patients.

In our study, even though in the groups treated with MPA compared to the control group, a greater number

Table 3 Comparison of clinical outcomes between study groups

Variable			MPA ($n=27$)	Placebo ($n=23$)	*P*-Value
NIV Days	Mean ± SD		6.37 ± 1.88	7.26 ± 1.86	0.62
Hospital LOS			9.63 ± 3.11	9.30 ± 2.93	0.99
ICU LOS			6.60 ± 2.50	6.29 ± 3.49	0.18
ICU Admission		N (%)	10 (37)	7 (30.4)	0.62
Cause of ICU admission	COPD Exacerbation		6 (60)	5 (71.4)	0.45
	CVA		0 (0.0)	1 (14.3)	
	GIB		0 (0.0)	1 (14.3)	
	Empyema		1 (10)	0 (0.0)	
	ACS		1 (10)	0 (0.0)	
	AKI		1 (10)	0 (0.0)	
	PTE		1 (10)	0 (0.0)	
Intubation			4 (14.8)	1 (4.3)	0.22
Mortality			2 (7.4)	1 (4.3)	0.56
Weaning			11 (40.7)	9 (39.1)	0.90

LOS: Length of Stay; NIV: Non Invasive Ventilation; MPA: Medroxyprogesterone Acetate; CVA: Cerebrovascular Accident; GIB: Gastrointestinal Bleeding; ACS: Acute coronary syndrome; AKI: Acute Kidney Injury; PTE: Pulmonary Thromboembolism

of patients succeeded in early weaning from NIV, there was no significant difference between the two groups in this regard, and the total weaning rate was similar in the two groups. The results in other studies about using MPA in weaning from the ventilator have not been promising either. Alizadeh et al. showed that the administration of MPA in intubated patients was not associated with significant changes in the amount of blood gas parameters [30]. Also, there was no significant difference in the weaning rate from the NIV, the length of hospital stay, and the mortality rate in the group receiving MPA; however, the weaning duration decreased by 1.429 days.

Previous studies show the positive effects of MPA in improving the laboratory parameters of hypercapnic COPD patients. Dolly et al. showed in an RCT that the administration of 60 mg of MPA in COPD patients for one month leads to an improvement in oxygenation and a decrease in PCO2 level in the awake state, but these effects were not seen in the sleep state [25]. It should be noted that the sample size used in this study was small, but the dose and duration of drug use were more than our study. Similar results have been seen in other studies about the effectiveness of MPA in COPD patients [16, 32, 33]. It should be remembered that these studies were conducted in chronic stable hypercapnic COPD patients. In addition to the difference in the dose and duration of drug administration, this important point may have been effective in the difference between the results of this study and previous studies.

It has been shown that the mechanism of hypercapnia in COPD patients in stable condition and acute exacerbation differs. The results of the studies on the state of respiratory drive in stable COPD patients with hypercapnia have been contradictory. Despite the increased respiratory drive reported in some studies [34–36], some evidence points to a decreased drive of the respiratory center as one of the causes of chronic hypercapnia in these patients [37, 38]. It needs to be clarified whether the increase in respiratory drive in these patients is proportional to the increase in their respiratory work [34]. The improvement of blood gas status with respiratory stimulating drugs is probably due to the stimulation of the respiratory center and the creation of hyperventilation in these patients. In exacerbation, hyperactivity of the respiratory drive is observed in the clinics as tachypnea in COPD patients [37, 39]. In fact, in the acute exacerbation of the disease, the deterioration of V/Q mismatch, bronchospasm, and hypersecretion leads to increased respiratory work in these patients [37, 40–42]. The increase in respiratory work leads to fatigue of the respiratory muscles, which cannot effectively respond to the increased impulses sent from the respiratory center [39]. Therefore, in these patients with increased respiratory drive activity, more stimulation with drugs that stimulate the respiratory center does not help, and this lack of drug response was also seen in our study. In this situation, reducing the workload of exhausted respiratory muscles by positive pressure ventilation plays a major role in improving the performance of the respiratory system and the resolution of hypercapnia in these patients [43]. For this reason, an additional response from respiratory stimulant drugs may not be seen in patients under invasive or noninvasive mechanical ventilation. Therefore, conducting more RCTs with a larger sample size is necessary to understand this issue better.

Limitation

This study has several limitations. The low sample size may have contributed to the results despite the higher sample size than many previous studies. In addition, we did not have any information about blood gas parameters and PCO2 status of patients in stable condition

before entering the study, and the presence or absence of chronic hypercapnia may have been effective in the results obtained from this study. The last point is that we did not include patients with very severe exacerbation of COPD requiring hospitalization in the ICU. Patients were admitted and treated in the non-ICU department. In this situation, they may have yet to receive complete and direct nursing care. Due to our hospital facilities, we had to admit patients in non-ICU departments.

Conclusion

Based on this study's findings, administration of medroxyprogesterone acetate in hypercapnic exacerbated COPD patients treated with NIV did not improve laboratory and clinical parameters. Due to the limited available evidence, subsequent RCT studies with a larger sample size are recommended.

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Author contributions
F.S., M.G.J., and A.S. were involved in the conception and design of the study. F.M. and M.M. prepared the placebo. M.G.J. and M.M. evaluated the patients and collected the data. F.S. and M.G.J. analyzed the data and drafted the first manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
All experimental protocols were approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1400.291). All methods were performed following relevant guidelines and regulations. This study was also approved by the Iranian Registry of Clinical Trials (IRCT20190810044500N21, 01/02/2022). Written informed consent was obtained from every participant before administrating any study intervention. The participants did not receive a monetary stipend.

Consent for publication
Consent for publication was agreed upon in the written consent forms signed by patients.

Competing interests
The authors declare no competing interests.

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References

1. Tamondong-Lachica DR, Skolnik N, Hurst JR, Marchetti N, Rabe APJ, Montes de Oca M et al. GOLD 2023 update: implications for clinical practice. Int J Chronic Obstr Pulm Dis. 2023;745–54.
2. 이영현. GOLD (Global Initiative for chronic obstructive lung disease) 2003 update 무엇이 달라졌나? 대한내과학회지. 2003;65(5):502–10.
3. Scaramuzzo G, Ottaviani I, Volta CA, Spadaro S. Mechanical ventilation and COPD: from pathophysiology to ventilatory management. Minerva Med. 2022;113(3):460–70.
4. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
5. Akbaş T, Güneş H. Characteristics and outcomes of patients with chronic obstructive pulmonary disease admitted to the intensive care unit due to acute hypercapnic respiratory failure. Acute Crit Care. 2023;38(1):49–56.
6. Dres M, Tran TC, Aegerter P, Rabbat A, Guidet B, Huchon G, et al. Influence of ICU case-volume on the management and hospital outcomes of acute exacerbations of chronic obstructive pulmonary disease*. Crit Care Med. 2013;41(8):1884–92.
7. Ferré A, Thille AW, Mekontso-Dessap A, Similowski T, Legriel S, Aegerter P, et al. Impact of corticosteroids on the duration of ventilatory support during severe acute exacerbations of chronic obstructive pulmonary disease in patients in the intensive care unit: a study protocol for a multicentre, randomized, placebo-controlled, double-blind trial. Trials. 2023;24(1):231.
8. Wagenaar M, Vos PJ, Heijdra Y, Teppema L, Folgering H. Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(5):1130–7.
9. Comellini V, Pacilli AMG, Nava S. Benefits of non-invasive ventilation in acute hypercapnic respiratory failure. Respirology. 2019;24(4):308–17.
10. Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, et al. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: a randomized clinical trial. JAMA. 2016;315(5):480–8.
11. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003;326(7382):185.
12. Plant P, Owen J, Elliott M. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355(9219):1931–5.
13. Hess DR. Noninvasive ventilation for Acute Respiratory FailureDiscussion. Respir Care. 2013;58(6):950–72.
14. Bales MJ, Timpe EMJAP. Respiratory stimulant use in chronic obstructive pulmonary disease. 2004;38(10):1722–5.
15. Bardsley PJT. stimulant? Chronic respiratory failure in COPD: is there a place for a respiratory 1993;48(8):781.
16. Saaresranta T, Aittokallio T, Utriainen K, Polo O. Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease. Respir Res. 2005;6(1):1–12.
17. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. J Appl Physiol. 1992;73(2):393–404.
18. Bales MJ, Timpe EM. Respiratory stimulant use in chronic obstructive pulmonary disease. Ann Pharmacother. 2004;38(10):1722–5.

19. Edelman AB, Cherala G, Stanczyk FZJC. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. 2010;82(4):314–23.
20. Poojary N, Capoor IA, Kundar MJJP, Sciences M. Medroxyprogesterone Acetate as a Respiratory Stimulant in Hypercapnic COPD, Postmenopausal COPD, Obesity Induced Hypoventilation, Obstructive Sleep Apnea, and Polycythemia. 2022;5(5):1–8.
21. Pietrosimone BG, Saliba SA, Hart JM, Hertel J, Ingersoll CD. Contralateral effects of disinhibitory TENS on quadriceps function in people with knee osteoarthritis following unilateral treatment. North Am J Sports Phys Therapy: NAJSPT. 2010;5(3):111.
22. Skatrud JB, Dempsey JA, Iber C, Berssenbrugge A, Thomas G, Schultze B. Correction of CO2 retention during sleep in patients with chronic obstructive pulmonary diseases. Am Rev Respir Dis. 1981;124(3):260–8.
23. CW ZJJLCM. Effects of progesterone on chemosensitivity in normal man. 1978;92:262–9.
24. Skatrud JB, Dempsey JA. Relative effectiveness of acetazolamide versus medroxyprogesterone acetate in correction of chronic carbon dioxide retention. Am Rev Respir Dis. 1983;127(4):405–12.
25. Dolly FR, Block AJ. Medroxyprogesterone acetate and COPD. Effect on breathing and oxygenation in sleeping and awake patients. Chest. 1983;84(4):394–8.
26. Daskalopoulou E, Patakas D, Tsara V, Zoglopitis F, Maniki E. Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease. Thorax. 1990;45(9):666–9.
27. Hill NS. Where should noninvasive ventilation be delivered? Respir Care. 2009;54(1):62–70.
28. Fontana V, Santinelli S, Internullo M, Marinelli P, Sardo L, Alessandrini G, et al. Effect of acetazolamide on post-NIV metabolic alkalosis in acute exacerbated COPD patients. Eur Rev Med Pharmacol Sci. 2016;20(1):37–43.
29. Fromer L, Cooper CB. A review of the GOLD guidelines for the diagnosis and treatment of patients with COPD. Int J Clin Pract. 2008;62(8):1219–36.
30. Alizadeh Z, Sahebnasagh A, Hadadzadegan N, Mohammadi F, Saghafi F. Effects of Donepezil and Medroxyprogesterone Versus Placebo on Weaning in adult patients with non-pulmonary etiologies receiving invasive mechanical ventilation: a triple-blind Randomized Clinical Trial. Front Pharmacol. 2021;12:735594.
31. Abbasi S, Farsaei S, Fazel K, Golzari SE, Mahmoodpoor A. Can Donepezil facilitate weaning from mechanical ventilation in difficult to wean patients? An interventional pilot study. DARU J Pharm Sci. 2015;23:1–8.
32. Skatrud JB, Dempsey JA, Bhansali P, Irvin C. Determinants of chronic carbon dioxide retention and its correction in humans. J Clin Investig. 1980;65(4):813–21.
33. Delaunois L, Delwiche J-P, Lulling J. Effect of medroxyprogesterone on ventilatory control and pulmonary gas exchange in chronic obstructive patients. Respiration. 1985;47(2):107–13.
34. Bardsley P. Chronic respiratory failure in COPD: is there a place for a respiratory stimulant? Thorax. 1993;48(8):781.
35. Sorli J, Grassino A, Lorange G, Milic-Emili J. Control of breathing in patients with chronic obstructive lung disease. Clin Sci Mol Med. 1978;54(3):295–304.
36. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne J-P. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1980;122(2):191–9.
37. Csoma B, Vulpi MR, Dragonieri S, Bentley A, Felton T, Lázár Z, et al. Hypercapnia in COPD: causes, consequences, and therapy. J Clin Med. 2022;11(11):3180.
38. Lourenço RV, Miranda JM. Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. N Engl J Med. 1968;279(2):53–9.
39. O'donnell D, Parker C. COPD exacerbations· 3: pathophysiology. Thorax. 2006;61(4):354–61.
40. Torres A, Reyes A, Roca J, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. Am Rev Respir Dis. 1989;140(5):1246–50.
41. Fleury B, Murciano D, Talamo C, Aubier M, Pariente R, Milic-Emili J. Work of breathing in patients with chronic obstructive pulmonary disease in acute respiratory failure. Am Rev Respir Dis. 1985;131(6):822–7.
42. Barberà JA, Roca J, Ferrer A, Félez MA, Díaz O, Roger N, et al. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J. 1997;10(6):1285–91.
43. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Reviews. 2004(3).

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