ORIGINAL ARTICLE

Evaluation of the effectiveness of medroxyprogesterone on blood gases and short-term hospital outcomes in patients with chronic obstructive pulmonary disease treating with noninvasive ventilation: A randomized clinical trial

Somayeh Sadeghi[1,2], Farzin Ghiasi[3], Mohammad Emamiardestani[3], Mina Nickpour[3,4], Roham Gholami[5], Mohammad Saeid Khaksar[3], Masoud Mansouri[3]

[1]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Immunodeficiency Research Center, AL-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Internal Medicine, School of Medical Sciences, Alborz University of Medical Sciences, Karaj, Alborz, Iran, [5]Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Background: In the present study, we aimed to evaluate the effects of medroxyprogesterone on hospital short clinical outcomes and ABG parameters in patients with chronic obstructive pulmonary disease (COPD) exacerbation under treatments with noninvasive ventilation (NIV) treated with progesterone 15 mg in comparison with placebo. **Materials and Methods:** This is a double-blinded clinical trial that was performed in 2020–2021 in Isfahan, Iran, on 60 patients with COPD exacerbation that require NIV. All patients received short-acting beta-agonists, short-acting anticholinergics, systemic corticosteroids, and NIV. Patients in the intervention group received tablets of progesterone 15 mg, every 6 h for 5 days and the control group received a placebo; patients in both groups received routine clinical cares. We collected data regarding the days requiring NIV, hospitalization duration, intubation, intensive care unit (ICU) admission, and death. Furthermore, blood pH, PCO2, O2 saturation, dyspnea score, and NIV hours usage per day were evaluated at the time of admission, 3 and 5 days during admission. **Results:** Hospital short clinical outcomes were not differently distributed between the two groups ($P > 0.05$). Comparing two groups during hospitalization in terms of short clinical outcomes including duration hospitalization, using NIV per day, ICU admission rate, and need to intubation showed that they are comparable ($P > 0.05$). PH in both groups improved during follow-up ($P < 0.001$) and patients in intervention groups showed higher improvement ($P = 0.006$). Mean PCO2 decreased significantly in the intervention group ($P < 0.001$) but not in the control group ($P = 0.198$) and totally intervention showed significant improvement in PCO2 compared with the control group ($P = 0.047$). Although mean O2 saturation was increased in both groups during follow-up period ($P < 0.001$, for both groups), two groups showed comparable ($P = 0.910$). Mean NIV using (hours/day) was decreased significantly in the intervention group ($P = 0.023$); however, it was not significantly higher than that was seen in the control group ($P = 0.706$). The mean dyspnea score was decreased in both groups ($P < 0.001$), although a greater decrease was seen in the intervention group ($P < 0.001$). **Conclusion:** Administration of medroxyprogesterone in patients with COPD exacerbation that required NIV was associated with significant improvements in blood pH, PCO2, dyspnea, and daily duration of NIV using after 3 and 5 days following hospitalization.

Key words: Chronic obstructive pulmonary disease, medroxyprogesterone, noninvasive ventilation

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Address for correspondence: Dr. Mina Nickpour, Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: minanickpour@yahoo.com

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is recognized as a common, preventable, and treatable disease with persistent obstructive airflow involvement of the airways.[1] According to recent reports, about 6% of the population suffers from some degree of the disease due to increased smoking, occupational exposure, and air pollution.[2] It has also been reported that COPD is one of the leading causes of death due to pulmonary diseases worldwide.[3]

Hospitalization due to acute COPD exacerbation is one of the leading causes of death in these patients.[4,5] Treatment for these episodes is relatively standard and includes controlled oxygen therapy, high doses of beta-agonist and/or anticholinergic drugs, systemic corticosteroids, and ventilator support if needed.[6]

Noninvasive ventilation (NIV) is prescribed to patients with COPD if pH < 7.35, pCO2 > 45, and respiratory rate >23 are still present after the use of bronchodilators and controlled oxygen therapy.[7] For NIV, full-face masks are usually used, and nebulized bronchodilators should be prescribed normally during rest periods and NIV intervals.[8] Proper use of NIV in a hypercapnic patient can clearly improve the outcome of COPD exacerbation patients.[9,10]

Previous research has indicated that hyperventilation could occur in women during pregnancy or in the luteal phase of the menstrual cycle, and studies have confirmed a direct link between circulating endogenous progesterone levels and increased ventilation.[11,12] Due to the lipophilic nature of steroid hormones, including progesterone, these hormones have the ability to cross the blood–brain barrier and this property leads to their effect on respiratory-stimulating receptors in the hypothalamus and brainstem. Based on this and other studies, the effect of medroxyprogesterone on sleep apnea was confirmed. In fact, endogenous progesterone and its metabolites affect the gamma-aminobutyric acid and N-methyl-D-aspartate receptors throughout the central nervous system and spinal cord and release these respiratory stimuli as were seen in animals.[13-15]

Thus, we decided to evaluate the effects of medroxyprogesterone on artrial blood gas (ABG) parameters and short-term hospital outcomes in exacerbated COPD patients who is required NIV.

MATERIALS AND METHODS

This is a multicenter double-blinded clinical trial that was performed in 2020–2021 at Isfahan province.

Enrollment of the patients (intervention and control) for this clinical trial was done in four hospitals that all of them affiliated with Isfahan University of Medical Sciences. The current study was conducted on patients with COPD exacerbation who require NIV. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences. Ethics code: IR.MUI.MED REC.1399.654.

Patient selection

The diagnosis of COPD exacerbation was defined as any exacerbation of respiratory symptoms that lead to requiring additional treatments, which could include any of the symptoms of aggravation of dyspnea (based on the Borg scale), increased sputum volume, and a change in the nature of sputum.[16] NIV requiring indications also included at least one of the followings:

1. Respiratory acidosis (PaCO2 ≥ 45 mmHg and arterial PH ≤ 7.35)
2. Stable hypoxemia despite adjuvant oxygen therapy
3. Severe dyspnea with clinical signs of respiratory muscle fatigue or increased respiratory function, such as the use of accessory respiratory muscles, inconsistent abdominal movements during respiration, or retraction of intercostal spaces.

The inclusion criteria were age between 30 and 80 years, COPD patients with exacerbation (having two of the three criteria of increasing dyspnea, increasing the volume of sputum, and changing the color of sputum-like purulence sputum), requiring NIV, and signing the written informed consent to participate in this study. The exclusion criteria were having NIV contraindications, requiring mechanical ventilation by the time of admission, having a current or history of thromboembolic diseases, presence of active thrombophlebitis, history of cerebrovascular disease, history of myocardial infarction and stroke, deformity of the face or chest, neuromuscular diseases and chest disorders, unexplained vaginal bleeding, hepatic diseases, pregnancy, history of breast cancer, or any estrogen- or progesterone-dependent tumor, history of allergy to hormonal drugs containing progesterone, decreased level of consciousness, pneumothorax, and stable and frequent vomiting.

The sample size was determined based on the following formula to detect standard effect size detection ($\Delta = 0.6$) for the main variables of the study,[17] i.e., ABG between the two groups, assuming the type one error rate 5% ($z = 1.96$) and statistical power of 80% ($z = 0.84$) resulted in 35 patients per each group (φ=1).

$$n = \left(\frac{1+\varphi}{\varphi}\right)\frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{\Delta^2} + \frac{Z^2_{1-\alpha/2}}{2(1+\varphi)}$$

Primary outcomes

The primary outcome of this study was evaluating the effect of medroxyprogesterone on blood gas parameters, especially blood pH, PCO2, and O2 saturation on COPD exacerbation.

Secondary outcomes

Our secondary outcomes were scores of dyspnea, days requiring NIV, duration of NIV usage each day, hospitalization duration, intubation, and intensive care unit (ICU) admission.

Procedure and assessment of variables

Patients were recruited based on the inclusion and exclusion criteria and were randomly divided into two groups (intervention and control; 1:1) using permuted block randomization of size 4. At the beginning, we collected data of the patients including age, gender, body mass index (BMI), smoking (pack per year), and the frequency of COPD exacerbation each year. Patients in both groups received standard treatments of COPD exacerbation phase based on GOLD guidelines[18] such as bronchodilators, systemic corticosteroids (prednisolone, 30–40 mg daily), antibiotics, and NIV. In addition to standard treatment, Group A (interventional group) received tablets of progesterone 15 mg, every 6 h for 5 days and Group B (control group) received placebo tablets with a similar shape to progesterone tablets that were produced in Isfahan University of Medical Sciences, School of Pharmacy and Pharmaceutical Sciences, and Pharmaceutical Sciences Research Center.

Our team collected data regarding the days requiring NIV, duration of NIV usage each day, hospitalization duration, intubation, and ICU admission. By the time of admission, after 3 and 5 days, a blood sample was collected from all cases to evaluate the ABG parameters including blood pH and PCO2. Capillary oxygenation saturation (SOP2) was also assessed for all cases.

Furthermore, in all patients, the dyspnea was checked before starting treatment and after 3 and 5 days through modified Borg dyspnea. Borg score is a criterion for classifying a patient's dyspnea that includes 10 points. The validity and reliability of this score in COPD patients were 0.76 and 0.7, respectively.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) is a statistical software suite developed by International Business Machines Corporation (IBM), American multinational technology company headquartered in Armonk, New York version 24. Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage). The normality of continuous variables was checked using the Shapiro–Wilk test and Q-Q plot. Continuous normally distributed variables were compared between two groups using independent samples *t*-test, whereas nonnormal data using Mann–Whitney *U* test and categorical variables were compared between groups using Chi-squared or Fisher's exact tests. Within and between-group comparisons in terms of change in blood pH, PCO2, O2 saturation, dyspnea score, and NIV hours usage per day were evaluated at the time of admission, 3 and 5 days during admission using repeated measures analysis of variance (ANOVA). The sphericity assumption was checked using Mauchly's test. When this assumption was violated, a multivariate approach was adopted. During repeated measures ANOVA when two groups were significantly different in terms of the baseline value of parameters, these values were adjusted as confounders. $P < 0.05$ was considered as a significance threshold.

RESULTS

In the present study, 70 patients were recruited based on the criteria and were divided into two groups each containing 35 patients. During the study, 10 cases were excluded due to decreased level of consciousness ($N = 4$) and NIV intolerance ($N = 6$). At the end, data of 60 patients with COPD exacerbation were analyzed. The CONSORT flow chart is indicated in Figure 1.

The study population consisted of 8 females (13.3%) and 52 males (86.7%) with the mean age of 64.36 ± 11.20 years. We found that there were no significant differences between intervention and control groups in terms of gender ($P = 0.706$), age ($P = 0.273$), BMI ($P = 0.796$), smoking habits ($P = 0.791$), and the frequency of COPD exacerbation per year ($P = 0.587$) [Table 1].

Comparing two groups during hospitalization in terms of short clinical outcomes including duration

Table 1: Comparison of demographic data between groups

	Intervention (*n*=30)	Control (*n*=30)	*P*
Sex			
Female	5 (16.7)*	3 (10.0)	0.706[a]
Male	25 (83.3)	27 (90.0)	
Age	67.1±13.8	62.6±9.7	0.273[b]
BMI	26.14±4.41	26.54±6.47	0.796[b]
Smoking (p/y)	32.1±11.3	33.6±15.9	0.791[b]
COPD exacerbations/year	0.8±1	0.7±1.1	0.587[b]

*Continuous and categorical data are represented by mean±SD and *n* (%); [a]Chi-square test; [b]Independent samples *t*-test or Mann–Whitney *U*-test. SD=Standard deviation; BMI=Body mass index; COPD=Chronic obstructive pulmonary disease

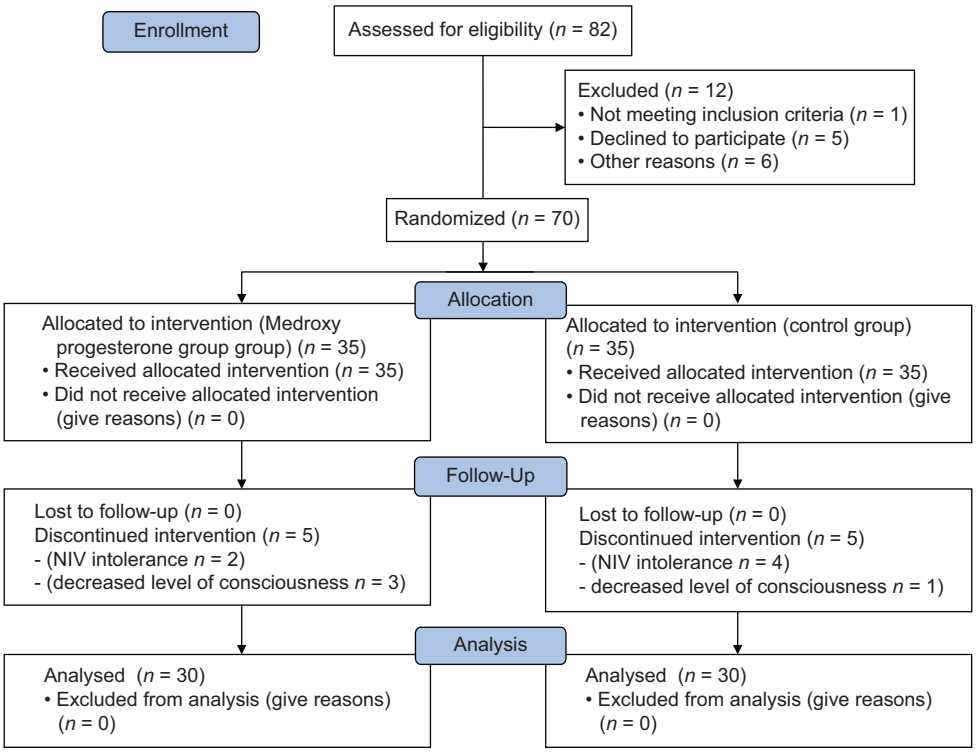

Figure 1: The CONSORT flow chart of the study

Table 2: Comparison of different hospital short clinical outcomes between two groups

	Intervention (*n*=30)	Control (*n*=30)	*P*
Hospitalization days*	6±2.8	6.4±2.1	0.567[a]
NIV days*	5.8±2.7	5.7±2.3	0.866[a]
Intubation			
No	30 (100)	29 (96.7)	>0.99[b]
Yes	0	1 (3.3)	
ICU			
No	27 (90.0)	26 (86.7)	>0.99[b]
Yes	3 (10)	4 (13.3)	

*Continuous and categorical data are represented by mean±SD and *n* (%); [a]Chi-square or Fisher's exact test; [b]Independent samples *t*-test. NIV=Noninvasive ventilation; SD=Standard deviation; ICU=Intensive care unit

hospitalization ($P = 0.567$), using NIV per day ($P = 0.866$), ICU admission rate ($P > 0.99$), and need to intubation ($P > 0.99$) showed that they are comparable [Table 2].

We also compared two groups in terms of ABG parameters and clinical situation during the hospitalization. Repeated measures ANOVA showed that the mean of PH in both groups improved during follow-up ($P < 0.001$; for both) and patients in intervention groups showed higher improvement generally than the control group ($P = 0.006$)) as well as in 3 ($P = 0.02$) and 5 ($P = 0.001$) days after admission. Mean PCO2 decreased significantly in the intervention group ($P < 0.001$) but not in the control group ($P = 0.198$) and total intervention showed significant improvement in PCO2 compared with the control group ($P = 0.047$). Although mean O2 saturation was increased in both groups during follow-up period ($P < 0.001$, for both groups), two groups showed comparable status in terms of this parameter ($P = 0.910$). Mean NIV using (hours/day) was decreased significantly in the intervention group ($P = 0.023$); however, it was not significantly higher than that was seen in control group ($P = 0.706$). Mean dyspnea score was decreased in both groups ($P < 0.001$, for both groups); however, a more significant decrease in the intervention group was seen ($P < 0.001$) [Table 3].

DISCUSSION

COPD exacerbation is accounted as an important clinical condition that might lead to mortality in patients. Serious efforts have been made to develop the best therapeutic guidelines and treatments for these patients. In the present study, we assessed the effectiveness of medroxyprogesterone treatments in patients with COPD exacerbation treated with NIV and observed that administration of these drugs led to improvements in blood pH within 3 and 5 days after admission. We should note that the blood pH improved significantly in both case and control groups but no significant difference between the two groups. Another important finding of our study was that we observed a more significant decreasing trend of PCO2 in patients of the case group compared to controls. This could be suggestive of the partial effects of medroxyprogesterone in this situation.

Table 3: Evaluation of arterial blood gas parameters and clinical situation during the hospitalization

	Intervention (*n*=30)	Control (*n*=30)	*P*
PH			
Day 0	7.25±0.08*	7.29±0.07	0.029[a]
Day 3	7.34±0.06	7.31±0.05	0.022[a]
Day 5	7.37±0.06	7.31±0.04	0.001[a]
P	<0.001[b]	0.013[b]	0.006[c]
PCO_2			
Day 0	74.52±14.26	6841±15.85	0.197[a]
Day 3	62.52±10.32	6371±14.30	0.889[a]
Day 5	56.79±10.02	62.90±14.87	0.130[a]
P	<0.001[b]	0.198[b]	0.047[c]
Saturation O_2			
Day 0	8345±5.96	8359±4.82	0.849[a]
Day 3	8665±4.85	87.45±2.92	0.881[a]
Day 5	88.65±4.31	88.14±2.80	0.646[a]
P	<0.001[b]	<0.001[b]	0.910[c]
NIV (h/day)			
Day 0	7.95±5.26	8.18±4.53	0.802[a]
Day 3	860±2.87	6.86±3.55	0.032[a]
Day 5	6.28±3.36	6.64±3.09	0.719[a]
P	0.023[b]	0.172b	0.706[c]
Dyspnea score			
Day 0	7.70±1.34	6.50±1.77	0.001[a]
Day 3	4.90±1.97	5.23±1.51	0.155[a]
Day 5	3.35±1.63	4.09±1.41	0.122[a]
P	<0.001[b]	<0.001[b]	0.001[c]

[a]Independent samples *t*-test; [b,c]Repeated measures ANOVA. *Continuous and categorical data are represented by mean±SD. NIV=Noninvasive ventilation; SD=Standard deviation; ANOVA=Analysis of variance

However, the other outcomes such as O2 saturation, hospitalization duration, intubation, NIV use, ICU admission, and death did not change after interventions compared to control and no significant difference.

In addition to a significant decreasing trend of PCO2 in patients of the case group compared to controls, we observed a significant improvement in dyspnea score in medroxyprogesterone compared to the placebo group.

Previously, some studies have assessed medroxyprogesterone administration and reported various results. In a study by Wagenaar *et al*. in The Netherlands, they evaluated the effects of acetazolamide, 250 mg bid, and medroxyprogesterone, 30 mg bid on daytime and nighttime blood gas values of patients with COPD exacerbation. Based on this study, the blood pH, and PCO2 improved in both groups significantly; however, the administration of medroxyprogesterone had no significant effects on O2 saturation and clinical outcomes, but acetazolamide was found to be more effective on blood gases in short-term treatment.[19] Another study also assessed the effects of medroxyprogesterone in this regard on 48 patients and reported that adding medroxyprogesterone to the management led to partial improvements in blood pH, but these effects were completely significant when combined with almitrine 50 mg bid. In this condition, both hypoxia and hypercapnia also improved significantly.[20] These results were in line with the findings of our study. Here, we showed that medroxyprogesterone could significantly improve the PCO2 and dyspnea score of patients after 3 and 5 days compared placebo group, but no other significant difference changes in clinical or laboratory conditions were shown in the comparison control group. It could be assessed that medroxyprogesterone administration is associated with slight significant effects on the clinical conditions, but these effects could magnify when associated with other agents. Wagenaar *et al*. showed short-term combined treatment with medroxyprogesterone and acetazolamide has a more favorable effect on day and nighttime blood gas values and chemical drive than single-drug treatment.[21]

The therapeutic effects of medroxyprogesterone have been evaluated in some other studies that reported significant effects of this drug on nocturnal breathing,[22] ventilatory control and pulmonary gas exchange,[23] and arterial blood gases,[24] but the important point of the current study is that we evaluated these effects on patients with COPD exacerbation that required NIV.

Another important point is that most of the mentioned studies have been conducted before 2010, and to the best of our knowledge, no recent study in the English literature has assessed this issue. The limitations of our study were the restricted study population and encounter during of study with COVID-19 pandemic that was resulted to prolong our study and limited us to evaluation respiratory volume of patients with spirometry. We believe that multicentric studies with larger populations could report different results. We also recommend that more attention should be given to the potential of medroxyprogesterone alone or in combination with other agents in the treatments of patients with COPD exacerbation.

CONCLUSION

Administration of medroxyprogesterone in patients with COPD exacerbation that required NIV was associated with significant improvements in blood PCO2 and dyspnea score after 3 and 5 days following hospitalization compared to the control group. No other significant effects were observed regarding blood gas parameters and clinical conditions of patients in comparison placebo group.

The results of our study support the use of medroxyprogesterone to improve decreasing PCO2 and improving dyspnea score,

but we should also notice that this drug had no significant effects on the outcomes of the patients. In general, we must pay attention to the side effect and financial burden of drug prescription on the health system.

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Conflicts of interest
Nil.

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