Received: 26 July 2019 | Revised: 8 October 2019 | Accepted: 9 December 2019

DOI: 10.1111/crj.13142

ORIGINAL ARTICLE

WILEY

Therapeutic effects of nebulized verapamil on chronic obstructive pulmonary disease: A randomized and double-blind clinical trial

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Abstract

Objectives: In this study, we assessed the clinical effect of inhaled verapamil on hospitalized COPD patients in a randomized and double-blind study.

Method: COPD patients randomly received 10 mg of inhaled verapamil or 4 cc nebulized distilled water (DW) as placebo.

Results: Twenty patients enrolled in each group with no difference in baseline characteristics. Mean age was 64.95 ± 8.9 and 66.9 ± 10.74 years in verapamil and control group; respectively, ($P > 0.05$).

The mean dyspnea score was 6.4 ± 1.2 and 6.2 ± 1.8 in the verapamil and control group, respectively and decreased to 4.9 ± 1.3 and 5.7 ± 1.8 after the intervention. The mean change in the verapamil group was significantly higher, (22.43% ± 10.6% vs 8.7% ± 12.1%), $P = 0.00$.

Unlike the control group, the FEV1 value in the verapamil group significantly increased and reached to 1.17 ± 0.4 L from 1.03 ± 0.4. There was a significant decrease in airway resistance in both groups after intervention. However, neither total lung capacity and residual volume nor forced vital capacity changed significantly. Moreover, oxygen saturation in the verapamil group changed 4.8% ± 2.5% and this improvement in the control group was 1.8 ± 1 ($P = 0.00$). Smoker subjects, ones with PAP more than 35 mm Hg and obese patients benefit from verapamil.

Conclusion: The beneficial impact of inhaled verapamil on the diminishing of dyspnea score along with its bronchodilatory effect would make this selective calcium blocker agent a therapeutic option in COPD.

1 | INTRODUCTION

COPD involves more than 10 percent of the population over 40 years old, and by 2020, will be the third leading causes of death.[1] In contrast to cardiac diseases, malignancy, and stroke, the mortality rate of COPD is rising significantly.[2,3] Even though this complex and heterogeneous disease is progressive and not fully reversible, it is manageable by proper therapeutic regiments. Effectual treatment of COPD can avoid further deterioration and complications, minimize symptoms, enhance exercise tolerance, and restrict the exacerbation rate.

COPD is a systemic inflammation disorder, and in severe stages, leads to pulmonary vasoconstriction because hypoxemia-induced modulation of reactive oxygen species and endothelial cells.[4-6] Subsequently, patients may experience pulmonary hypertension, ventilation-perfusion mismatch and cor-pulmonale or other comorbidities.[7]

From a physiologic point of view, bronchoconstriction via cholinergic tone along with loss of elasticity recoil and airways narrowing, impair lung function in COPD. Bronchodilators are one of the potential therapeutic options in COPD which can improve the airflow limitation via inducing airway smooth-muscle relaxation, clearing mucus and reducing airway wall edema.[8] Three major classes of bronchodilators are β2 agonists, anticholinergic and theophylline.[9] Several studies have been conducted to investigate various types of bronchodilators from a long-lasting point of view and concurrent administration. Anzueto and Miravitlles believe that the co-administration of bronchodilators could improve the efficacy and reduce complications associated with higher doses of one drug.[10]

Acute hypoxia causes an influx of intracellular calcium in smooth muscle cells of the pulmonary arterial wall.[11] Calcium antagonists block calcium ion entry into the cells; therefore, their vasodilatory effect and airway's muscle relaxant render them as an appropriate option for stable or acute exacerbation of COPD.

Moreover, considering the therapeutic effects of calcium channel blockers (CCBs) on secondary pulmonary hypertension and the high prevalence of this complication among COPD patients (from 5% to 90% in different population)[12-14] it has been suggested that CCBs can act via several pathways to reduce hypoxemia and cut the chain off.

In this regard, calcium antagonists such as Nifedipine mostly affect the peripheral vascular bed, yet verapamil acts in the same manner on both heart and periphery. Concerning the route of medication use, inhaled medications are more favorable than oral drugs owing to their fewer side effects and rapid onset of action. Moreover, controversy continues on the benefits of employing non-selective vasodilators in COPD regarding the increased ventilation/perfusion (V/Q) mismatch, short effectiveness and their cardiac side effects.[15] In fact research in this field is very dynamic and various CCBs with different dosage are under consideration.[16] In the case of using verapamil as a bronchodilator, COPD patients could benefit from the therapeutic effects of CCBs such as bronchodilation and pulmonary hypertension reduction. This study investigates the therapeutic effects of Nebulized Verapamil on Chronic Obstructive Pulmonary Disease.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was a double-blind randomized placebo-controlled clinical trial (IRCT20170210032478N2).

2.2 | Participants

2.2.1 | Inclusion criteria

All COPD patients, with the GOLD stage II, III and IV, in the exacerbation period who admitted in a tertiary university hospital in Tehran, Iran between August 2018 and December 2018. COPD Diagnosis was confirmed by one pulmonologist based on GOLD criteria.[17] COPD Exacerbation was defined as rapid deterioration in patient's condition from the stable state, requiring hospitalization.

2.2.2 | Exclusion criteria

Pregnant woman, Patients with advanced hepatic or renal failure or pulmonary disorders other than COPD, patients with high-grade Atrioventricular block, arrhythmia or QT interval disorders, Ejection Fraction (EF) less than 40%, previous verapamil sensitivity, Co-administration of β-adrenergic blocker drugs, and bradycardia.

2.2.3 | Measurements and data gathering

Demographics including age, sex, Body Mass Index (BMI); Baseline EF, Pulmonary Artery Pressure (sPAP using Echocardiography), history of cigarette smoking and duration of the disease were obtained.

Oxygen saturation was assessed using pulseoximetry before and 20 minutes after intervention completion. Modified 0-10 Borg scale was used to evaluate dyspnea intensity. Baseline and post-treatment pulmonary function test and body plethysmography were carried out (Ganshorn power cube LF8) to measure Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, Forced Expiratory Flow at 25%-75% of the pulmonary volume (FEF25-75), Total Lung Capacity (TLC), Residual Volume (RV), RV/TLC, airway resistance, thoracic gas volume (TGV) and Specific Resistance airway (sRAW).

The percent of change in the above-mentioned parameters was also calculated as (amount of change/original amount) × 100. The percent of changes were compared in obese patients (BMI more than 30 kg/m^2), Age more than 60 y/o and sPAP more than 35 mm Hg.

Furthermore, heart rate, as well as blood pressure, were monitored to assess any side effect of verapamil.

2.3 | Randomization

Participants were randomly divided into two groups of verapamil and placebo based on computer-generated random codes.

TABLE 1 Baseline characterizations of patients in the treatment and placebo group

Group Variable	Treatment (Verapamil)	Placebo (DW)	*P* value
Gender	Male	Male	0.677
	16 (80%)	17 (85%)	
Age	64.95 ± 8.994	66.90 ± 10.74	0.54
BMI	24.30 ± 4.77	26.2 ± 6.49	0.383
Borg scale	6.4 ± 1.2	6.2 ± 1.8	0.2
O_2_saturation	87.5 ± 2.6	88.3 ± 2.2	0.6
Disease duration	4.2 ± 3	5 ± 4.3	0.4
EF	49.2 ± 3.72	51.50 ± 3.28	0.05
PAP	37.25 ± 8.80	34.15 ± 12.20	0.3
FEV1			
Pred %	38.0 ± 13.74	41.4 ± 19.0	0.910
Actual (L)	1.036 ± 0.42	1.02 ± 0.59	0.9
FVC			
Pred %	54.3 ± 12.8	51.7 ± 20.37	0.632
Actual (L)	1.87 ± 0.62	1.73 ± 0.89	0.5
TLC			
Pred %	112.3 ± 18.9	101.2 ± 21.09	0.09
Actual (L)	6.65 ± 1.35	6.35 ± 1.80	0.5
RV			
Pred %	200.3 ± 50.24	177.5 ± 54.1	0.17
Actual (L)	4.32 ± 1.50	4.37 ± 1.108	0.9
Airway resistance			
Pred %	368.3 ± 183.82	499.75 ± 355.45	0.15
Actual (kPa/L/Sec)	1.241 ± 0.87	0.84 ± 5.40	0.07
TGV L			
Pred %	151.95 ± 44.94	169.4 ± 29.4	0.35
Actual (L)	5 ± 1.6	5.4 ± 1.2	
sRAW			
Pred %	579 ± 386	600 ± 399	0.93
Actual (kPa/L/Sec)	6.5 ± 4.3	6.8 ± 4.6	0.93
History of smoking	16 (80%)	17(85%)	0.6
HR beats/min	87.65 ± 14.80	85.25 ± 12.56509	0.5
Mean BP mm Hg	88 ± 11.8	90.8 ± 11.6	0.4
GOLD stage			
Stage II	3 (15%)	4 (20%)	0.2
Stage III	14 (70%)	8 (40%)	
Stage IV	3 (15%)	8 (40%)	

Abbreviations: BMI, body mass index; EF, ejection fraction; FEF25-75, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart ratePAP, pulmonary artery pressure; RV, residual volume; sRAW, specific resistance airway; TGV, thoracic gas volume; TLC, total lung capacity.

2.4 | Intervention

On the day of discharge, patients in verapamil group were administered 10 mg of the medication (4 cc, concentration of 2.5 mg/mL) through Ultrasonic Nebulizer CUN60 (CITIZEN, Japan) in 10 minutes. The Placebo group were administered 4 cc DW through the same Nebulizer. Both groups received standard treatment during the study.

2.5 | Ethical considerations

The study protocol was approved in the ethics committee of Imam Khomeini Hospital complex—Tehran University of Medical Sciences (code: IR.TUMS.IKHC.REC.1397.O89) and written informed consent form was obtained from all patients.

Patients were monitored during the study to detect any possible complication. All participating were enrolled in the study with no extra charge.

2.6 | Statistical analysis

All statistical analysis was performed using SPSS statistics software version 22.0. Data were expressed as mean ± SD or percent. Normal distribution of quantitative data were tested by Kolmogorov Smirnov, Mann-Whitney *U* test or *t* student test was used to analyze according to data distribution. To compare the results before and after intervention, paired test or Wilcoxon rank test and for categorical data, Pearson's chi-squared test was used for the analysis. A P value of < 0.05 was considered statistically significant and continence Interval was 95%.

3 | RESULTS

Forty patients completed the study. Baseline characteristics and demographic data are summarized in Table 1. The male/female ratio was 16/4 and 17/3 in the verapamil and DW group, respectively.

No significant difference was observed in age and sex distribution, GOLD stage, Borg scale, EF, sPAP, BMI and time of admission to discharge between the placebo and verapamil groups, Table 1.

The mean dyspnea score was 6.4 ± 1.2 and 6.2 ± 1.8 in the verapamil and control groups, respectively that reached to 4.9 ± 1.3 and 5.7 ± 1.8, respectively. Percent change in the verapamil group was significantly higher than the control group (22.43% ± 10.6% vs 8.7% ± 12.1%; $P = 0.00$) using student *t* test based on normal distribution Figure 1.

The number of patients in GOLD IV was 15% and 40% in verapamil and control group, respectively with no statistically difference using χ^2. However, splitting data indicated that among patients in GOLD IV, dyspnea score decreased 26.19 ± 8.57 in verapamil group and 8.97 ± 7.8 in control group ($P = 0.01$). This comparison was also significant in GOLD III. But no statistical difference was observed in GOLD II.

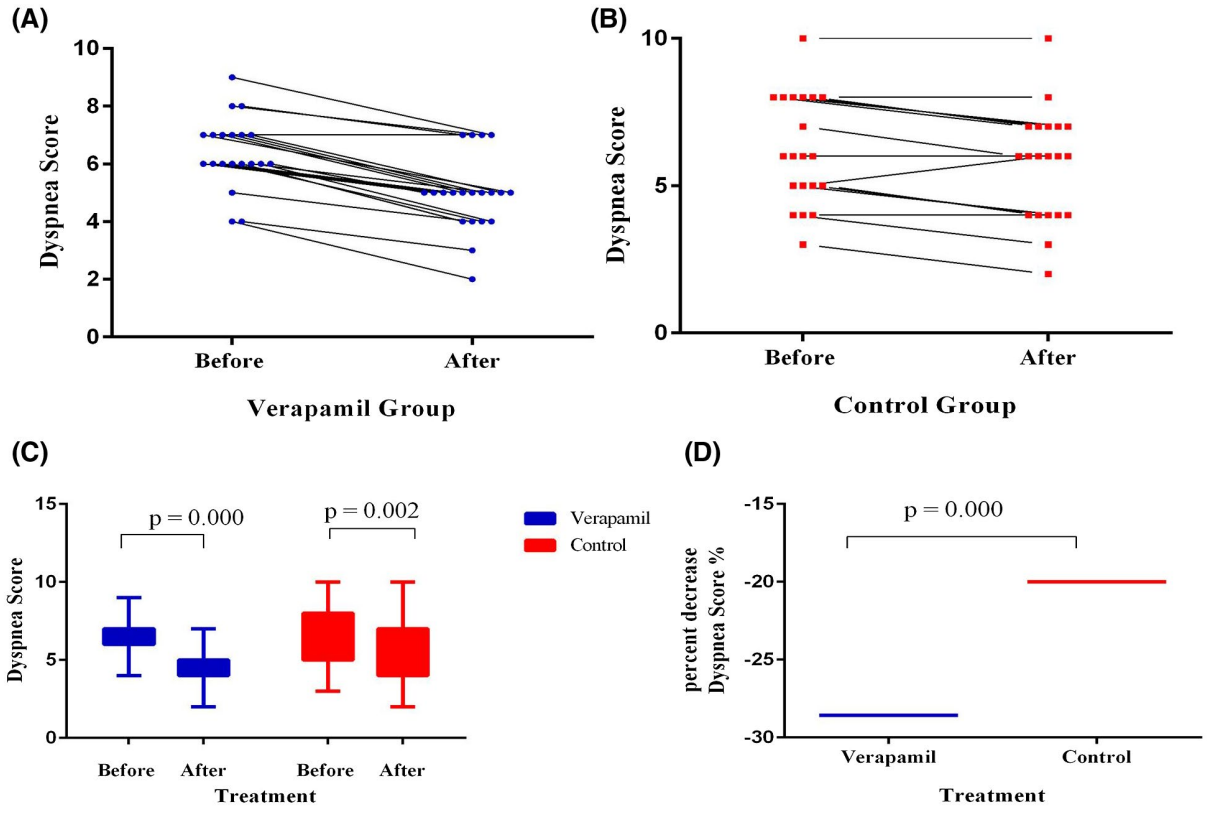

FIGURE 1 Mean dyspnea score in verapamil vs control group. A and B, Individual change in verapamil and DW group 20 minutes after the end of intervention. C, Post-treatment results indicated that dyspnea score significantly dropped in both intervention groups. D, The severity of decline was higher in the verapamil group compared to the DW group. Distilled Water (DW)

FEV1 change: A 12% improvement in FEV1-predicted and >200 cc increase in FEV1 was considered positive bronchodilation response.[18] In the verapamil group response rate was 20% and in the control group was 10% ($P = 0.37$), according to student *t* test based on normal distribution.

Figure 2 shows spirometric parameters before and after treatment. FEV1 was 1.03 ± 0.4 L vs 1.9 ± 0.4 L ($P = 0.00$) in the verapamil group before and after treatment and it was 1.02 ± 0.59 vs 1.09 ± 0.6 L ($P = 0.42$) in the control group using paired *t* test based on normal distribution. Also, the FEF 25-75 before and after verapamil was 18.5 ± 10.6 vs 22.3 ± 10.7; ($P = 0.02$). While in the control group FEF 25-75 was 20.6 ± 10.2 vs 21.7 ± 10.5, ($P = 0.27$), based on the results of paired *t* test Table 2.

There were no statistically significant differences in the plethysmograhic parameters before and after treatment (according to paired *t* test) except to airway resistance and sRAW (Table 2).

The rate of lung hyperinflation demonstrated by TGV more than 120% of predicted value[19] was 75% ($n = 5$) in verapamil group and 100% in control group with no significant change after both interventions.

As it has been depicted in Figure 3, post-treatment O_2 saturation was significantly higher in the verapamil group compare to the control group; 91.7% ± 2.8% vs 89% ± 1.9%, respectively, ($P = 0.02$), using paired *t* test.

Percent changes in variables after treatment with either verapamil or placebo are summarized in Table 3. The percentage of changes in FEV1 in the verapamil group was 2.5-fold higher among smoker patients compare to non-smokers. While in the control group, the percentage change in FEV1 was 15 times higher among non-smokers in comparison with smokers, $P = 0.01$ using student *t* test.

Table 4 shows outcome variables in the verapamil group in comparison with the control group according to cigarette smoking status. In smokers, FEV1- change; FEV1/FVC and FEF 25-75 significantly improved in the verapamil compare to the control group, but among nonsmokers subjects, there was no difference between verapamil and control group based on student *t* test.

Table 5 shows outcome variables in patients with PAP more than 35 mm Hg. Dyspnea score decreased 23.6% and 4.8% in verapamil vs control group, respectively ($P = 0.000$). Also, FEV1 increased 25.1 ± 21.8 vs 1.8% ± 1.3%, in

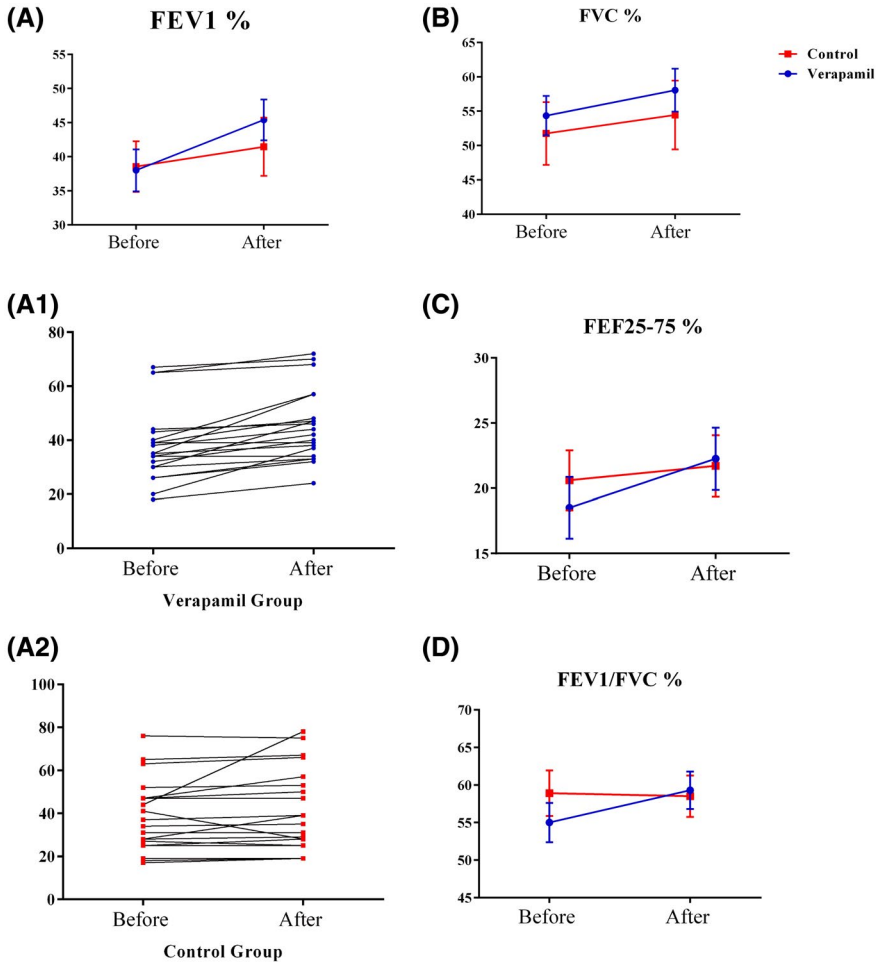

FIGURE 2 Spirometry parameters before and after treatment. A, A1, and A2, mean and individual change of FEV1 in both treatment groups. B, mean change of FVC before and after treatment. C, mean change of FEF 25-75 before and after treatment. D, mean change of FEV1/FVC before and after treatment. Verapamil significantly increased FEV1 and FEF 25-75. FVC change in both groups showed a similar improvement. Also FEV1/FVC change was not meaningful in both groups. FEF25-75, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

TABLE 2 Spirometric parameters after verapamil vs DW inhalation

Parameter	Intervention	Before intervention	After intervention	*P* value
FEV1				
	Verapamil (Mean ± SD)	Pred %: 38 ± 13.7 Actual (L): 1.036 ± 0.42	Pred %: 45.4 ± 13.4 Actual (L): 1.9 ± 0.4	***0.000***
	DW (Mean ± SD)	Pred %: 38.6 ± 16.5 1.02 ± 0.59	Pred %: 41.5 ± 19.1 1.09 ± 0.6	0.42
FVC				
	Verapamil (Mean ± SD)	Pred %: 54.4 ± 12.8 Actual (L): 1.87 ± 0.62	Pred %: 58.1 ± 14 Actual (L): 1.9 ± 0.6	0.65
	DW (Mean ± SD)	Pred %: 51.8 ± 20.4 Actual (L): 1.73 ± 0.89	Pred %: 54.5 ± 22.4 Actual (L): 1.8 ± 1.00	0.12
FEV1/FVC	Verapamil (Mean ± SD)	55 ± 11.7	59.3 ± 11.1	0.23
	DW (Mean ± SD)	58.9 ± 13.5	58.5 ± 12.3	0.25
FEF25_75				
	Verapamil (Mean ± SD)	Pred %: 18.5 ± 10.6 Actual (L): 0.5 ± 0.3	Pred %: 22.3 ± 10.7 Actual (L): 0.7 ± 0.4	***0.02***
	DW (Mean ± SD)	Pred %: 20.6 ± 10.2 0.6 ± 0.3	Pred %: 21.7 ± 10.5 0.6 ± 0.4	0.16
TLC				
	Verapamil (Mean ± SD)	Pred %: 112.3 ± 18.9 Actual (L): 6.65 ± 1.35	Pred %: 110.1 ± 15.2 Actual (L): 6.6 ± 1.3	0.54
	DW (Mean ± SD)	Pred %: 101.2 ± 21.1 Actual (L): 6.35 ± 1.80	Pred %: 107.1 ± 25.1 Actual (L): 6.3 ± 1.8	0.18
RV				
	Verapamil (Mean ± SD)	Pred %: 200.4 ± 50.2 Actual (L): 4.5 ± 1.3	Pred %: 191.5 ± 41.7 Actual (L): 4.3 ± 1.1	0.35
	DW (Mean ± SD)	Pred %: 177.5 ± 54.1 Actual (L): 4.1 ± 1.4	Pred %: 186 ± 62 Actual (L): 4.3 ± 1.5	0.6
RV/TLC	Verapamil (Mean ± SD)	176 ± 34.1	168.1 ± 20.5	0.3
	DW (Mean ± SD)	173.1 ± 26.1	168.2 ± 28	0.54
Airway_resistance				
	Verapamil (Mean ± SD)	Pred %: 368.4 ± 183.8 Actual kPa/L/Sec:1. 12 ± 0.59	Pred %: 265.7 ± 130.4 Actual kPa/L/Sec: 0.8 ± 0.4	***0.002***
	DW (Mean ± SD)	Pred %: 499.8 ± 355.5 Actual kPa/L/Sec: 1.5 ± 1.1	Pred %: 395.3 ± 261.8 Actual kPa/L/Sec: 1.2 ± 0.87	***0.006*** ***0.006***
TGV				
	Verapamil (Mean ± SD)	Pred %: 151.95 ± 44.94 Actual (L): 5 ± 1.6	Pred %: 154.8 ± 41.3 Actual (L): 5.11 ± 1.56	0.7
	DW (Mean ± SD)	Pred %: 169.4 ± 29.4 Actual (L): 5.4 ± 1.2	Pred %: 169.8 ± 28.2 Actual (L): 6.11 ± 1.5	0.8
sRAW				
	Verapamil (Mean ± SD)	Pred %: 579 ± 386 Actual kPa/L/ Sec: 6.5 ± 4.3	Pred %: 452.35 ± 332.9 Actual kPa/L/ Sec: 5.11 ± 3.7	***0.00***

(Continues)

TABLE 2 (Continued)

Parameter	Intervention	Before intervention	After intervention	*P* value
	DW (Mean ± SD)	Pred %: 600 ± 399 Actual kPa/L/Sec: 6.8 ± 4.6	Pred %: 511.7 ± 345 Actual kPa/L/Sec: 5.8 ± 3.8	***0.00***
MBP mm Hg	Verapamil (Mean ± SD)	88 ± 11.6	88.4 ± 10.8	0.65
	DW (Mean ± SD)	90.8 ± 11.6	91.6 ± 12.8	0.3
HR beat/min	Verapamil (Mean ± SD)	87.6 ± 14.8	87.5 ± 13.5	0.86
	DW (Mean ± SD)	85.2 ± 12.5	83.9 ± 10.4	0.28
Saturation %	Verapamil (Mean ± SD)	87.5 ± 2.6	91.7 ± 2.8	***0.000***
	DW (Mean ± SD)	88.3 ± 2.3	89 ± 1.9%	***0.000***

Note: Bold-Italic values indicate significant difference.

Abbreviations: DW, distilled water; FEF25-75, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; RV, residual volume; sRAW, specific resistance airway; TGV, thoracic gas volume; TLC, total lung capacity.

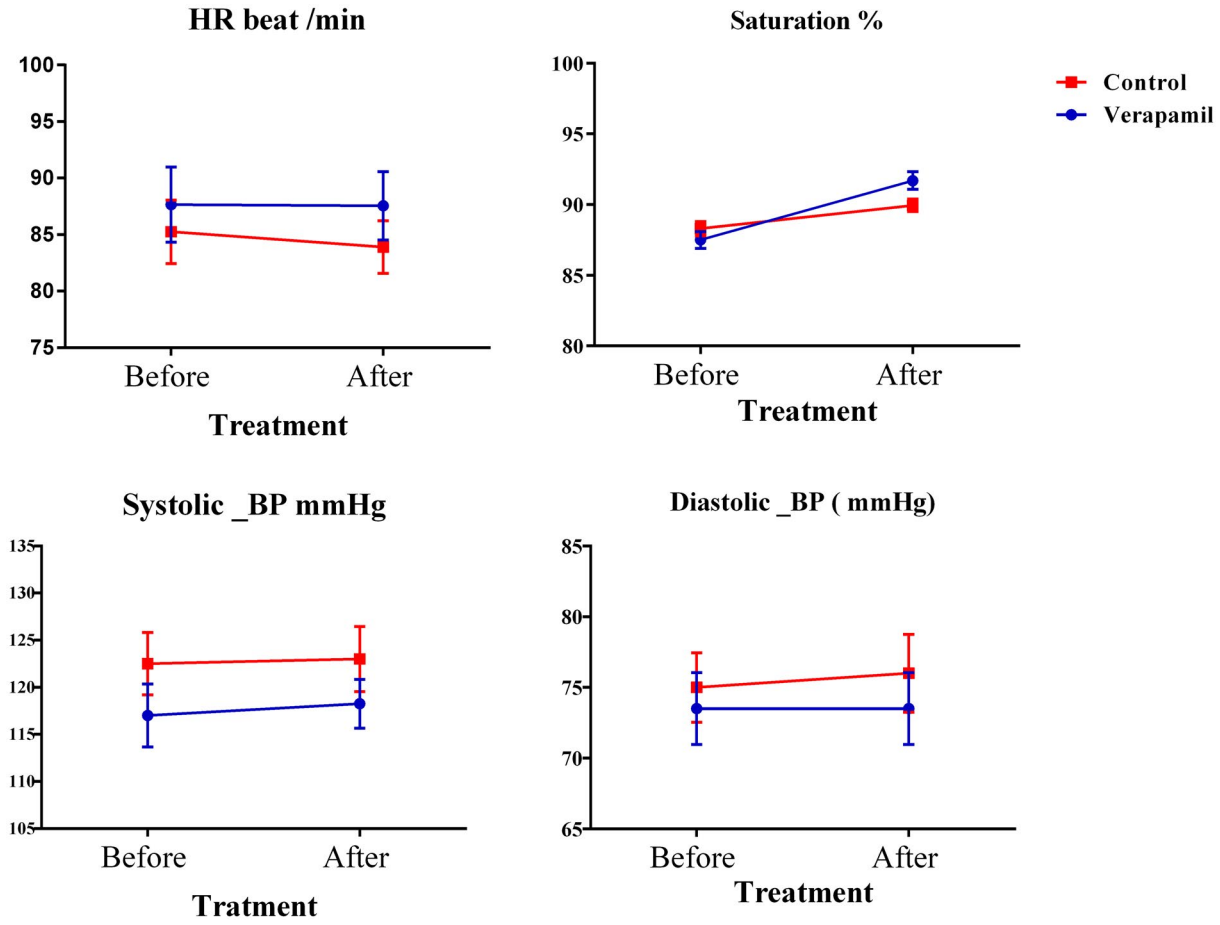

FIGURE 3 Changes in HR, oxygen saturation, blood pressure in patients in the verapamil and control group. Between-group analysis indicated that there was no significant difference in HR and blood pressure after the intervention. But post-treatment O_2 saturation was significantly higher in the verapamil group. Heart Rate (HR)

verapamil vs control group, respectively ($P = 0.000$) employing student *t* test (Table 5).

FEV1-change in subjects older than 60 years of age in the verapamil group was significantly higher than the control group, 21.2% ± 9.5% vs 7.1% ± 3.4%, ($P = 0.04$) while it was not statistically different in subjects younger than 60 years old although there was almost a similar trend.

Also, in patients with a BMI greater than 30 kg/m^2, dyspnea score reduced 23.6% and 9.3% in verapamil vs control group, respectively. Moreover, FEV1 increased by 23.2% and

TABLE 3 Percentage changes in the outcome variables after treatment with either verapamil or placebo

		Mean ± SEM	*P* value
	Intervention	**Pred %**	**Pred %**
FEV1-change	Verapamil	23.5 ± 5.1	*0.028*
	DW	7.7 ± 4.7	
FVC-change	Verapamil	10.0 ± 5.8	0.458
	DW	5.3 ± 2.4	
TLC-change	Verapamil	0.4 ± 5.1	0.345
	DW	6.2 ± 3.3	
RV-change	Verapamil	3.0 ± 9.8	0.786
	DW	6.0 ± 5.0	
Resistance-change	Verapamil	−23.4 ± 7.8	0.26
	DW	−12.0 ± 6.4	
FEF 25-75-change	Verapamil	29.4 ± 9.3	*0.04*
	DW	8.2 ± 6.01	
EEV1/FVC-change	Verapamil	9.6 ± 4.3	0.07
	DW	0.18 ± 2.7	
RV/TLC-change %	Verapamil	−1.5 ± 4.7	0.811
	DW	−2.7 ± 1.9	
TGV-change %	Verapamil	−0.6 ± 12.7	0.9
	DW	1.2 ± 15.4	
sRAW-change %	Verapamil	−18.6 ± 27.2	0.3
	DW	−9.3 ± 31.7	
Saturation-change %	Verapamil	4.8 ± 0.6	*0.000*
	DW	1.9 ± 0.3	
HR-change %	Verapamil	0.4 ± 1.9	0.572
	DW	−1.0 ± 1.7	
SBP-change %	Verapamil	1.8 ± 2.1	0.66
	DW	0.6 ± 1.7	
DBP-change %	Verapamil	0.1 ± 1.1	0.505
	DW	1.3 ± 1.3	

Note: Bold-Italic values indicate significant difference.

Abbreviations: DBP, diastolic blood pressure; DW, distilled water; FEF25-75, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; RV, residual volume; SBP, systolic blood pressure; sRAW, specific resistance airway; TGV, thoracic gas volume; TLC, total lung capacity.

5.2% in verapamil vs control group, according to student *t* test, Figure 4.

4 | DISCUSSION

In this study, the therapeutic effects of inhaled verapamil on hospitalized COPD patients were evaluated. Verapamil notably reduced the dyspnea score, improved oxygenation, FEV1, FEF 25-75 and airway resistance. Hypoxia correction is important in COPD exacerbation.[4] Prevalence of hypoxia (less than 88% oxygen saturation), dramatically dropped using inhaled verapamil (65% vs 5%) before and after verapamil and (45% vs 20%) before and after DW inhalation.

Regarding rapid effect of CCBs-nebulizer and its minimal systemic side effects, it is suggested as a preventive bronchodilator in such conditions.[20] In different conditions including histamine-induced bronchospasm, methacholine or allergen-induced bronchoconstriction CCBs in nebulized forms act as a preventive factor.[21] In this regard, Sharma and Pande conducted a clinical trial based on verapamil inhalation therapy in asthmatic patients and reported no significant increase in spirometry parameters.[22] However, our study indicated a considerable increase in FEV1 in the verapamil group. It is to be noted that in the placebo group, inhaled DW caused sputum dilution and may lead to better mucosal clearance and consequently reduction in the airway resistance. So, DW as the placebo may be a confounding factor.

Age over 60 years is a risk factor for COPD patients.[23] In the present study, in subjects more than 60 years old, verapamil inhalation improved spirometry parameters and dyspnea score, although younger patients showed similar changes with no statistical difference. As it has already been evaluated in large COPD patient populations, age is not a predictor of response to bronchodilator.[18,24]

Likewise, in patients with BMI more than 30, attenuation in airway resistance was higher in verapamil patients compared with that of the placebo group. Obesity has been associated with higher mortality in COPD. Veronika Müller showed a significantly higher BMI in COPD patients with reversible airway bronchoconstriction compared to non-reversible patients. In our study, FEV1 change was considerable in verapamil patients compared to control group.

As the PAP correlation diagram (Figure 4A) indicates, in the control group, with the increase in PAP, no notable improvement was observed regarding FEV1; on the contrary, in the verapamil group, the negative effect of PAP was corrected and by increasing PAP, a considerable change was observed in FEV1.

Given that systemic inflammation, pulmonary vasoconstriction, and polycythemia and endothelial dysfunction[25,26] expose COPD patients to pulmonary hypertension,[27] the therapeutic option which attenuates PAP can improve dyspnea score. In our study 12 (60%) patients in the verapamil group and 11 in the placebo group (55%) had a PAP higher than 35 mm Hg. Accordingly, almost half of patients had PAP > 35 mm Hg. In these cases, inhaled verapamil acts as a multifunctional agent as a bronchodilator and a pulmonary vasodilation.[28]

In our study, inhaled verapamil had no effect on heart rate and blood pressure, although some researchers believe in systemic vasodilation of CCBs. As mentioned by other studies, 20 mg verapamil can be given safely to COPD patients

TABLE 4 Percentage changes of the outcome variables in smoker vs nonsmoker patients

		Verapamil	Control	
	Smoking	**Mean % ± SD**	**Mean % ± SD**	***P* value**
FEV1_change	No	10.3 ± 9	36.4 ± 42.4	0.27
	Yes	26.8 ± 24.2	2.7 ± 10.5	***0.001***
FVC_change	No	7.6 ± 14.8	15.7 ± 16	0.52
	Yes	10.6 ± 28.2	3.5 ± 9.2	0.3
FEV1_FVC_change	No	3.4 ± 19.3	5.4 ± 25.8	0.9
	Yes	11.2 ± 20	−0.7 ± 9.5	***0.03***
FEF25-75	No	11 ± 30.2	30.2 ± 67	0.62
	Yes	34 ± 43.5	4 ± 13	***0.02***
TLC_change	No	−8.9 ± 9	−0.2 ± 12.9	0.33
	Yes	2.7 ± 24.7	7.3 ± 15.4	0.51
RV_change	No	−14.8 ± 9.3	−4.3 ± 17.2	0.34
	Yes	7.5 ± 48.2	7.9 ± 23.3	0.97
Resistance_change	No	−35 ± 34.8	−19.9 ± 19.7	0.47
	Yes	−20.5 ± 35.4	−10.6 ± 30.1	0.38
RV_TLC_change	No	−6.5 ± 5.3	−4.8 ± 4.6	0.67
	Yes	−0.2 ± 23.4	−2.3 ± 8.8	0.73
O_2 Saturatin_change	No	3.7 ± 2.5	0.7 ± 0.6	0.28
	Yes	5.1 ± 2.5	2.1 ± 1.2	0.319

Note: Bold-Italic values indicate significant difference.

Abbreviations: FEF, Forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

TABLE 5 Percentage changes of the outcome variables in patients with PAP more than 35 mm Hg

	Intervention	***N***	**Mean ± SD**	***P* value**
Dyspnea_change %	Verapamil	7	−23.6 ± 7.9	***0.003***
	DW	8	−4.8 ± 15.3	
FEV1_change %	Verapamil	7	25 ± 21.8	***0.009***
	DW	8	1.8 ± 16.1	
FVC_change %	Verapamil	7	0.6 ± 25.5	0.72
	DW	8	3.3 ± 8.2	
FEV1_FVCchange %	Verapamil	7	12.7 ± 26.7	.063
	DW	8	1.2 ± 9.6	
FEF_change %	Verapamil	7	35.2 ± 65.6	0.68
	DW	8	4.4 ± 14.7	
TLC_change %	Verapamil	7	−0.4 ± 6	***0.01***
	DW	8	15.8 ± 18	
RV_change %	Verapamil	7	4.9 ± 33.7	0.1
	DW	8	23.1 ± 24.8	
RV_TLC_change %	Verapamil	7	2.5 ± 29.9	0.9
	DW	8	1 ± 5.2	
Resistance_change %	Verapamil	7	−18.2 ± 39.2	0.5
	DW	8	−9.9 ± 32.8	
HR_change %	Verapamil	7	6 ± 3.5	***0.002***
	DW	8	2.2 ± 1.5	
O_2 Saturation_change %	Verapamil	7	1.6 ± 8.6	0.68
	DW	8	−1.6 ± 8.9	

Note: Bold-Italic values indicate significant difference.

Abbreviations: FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

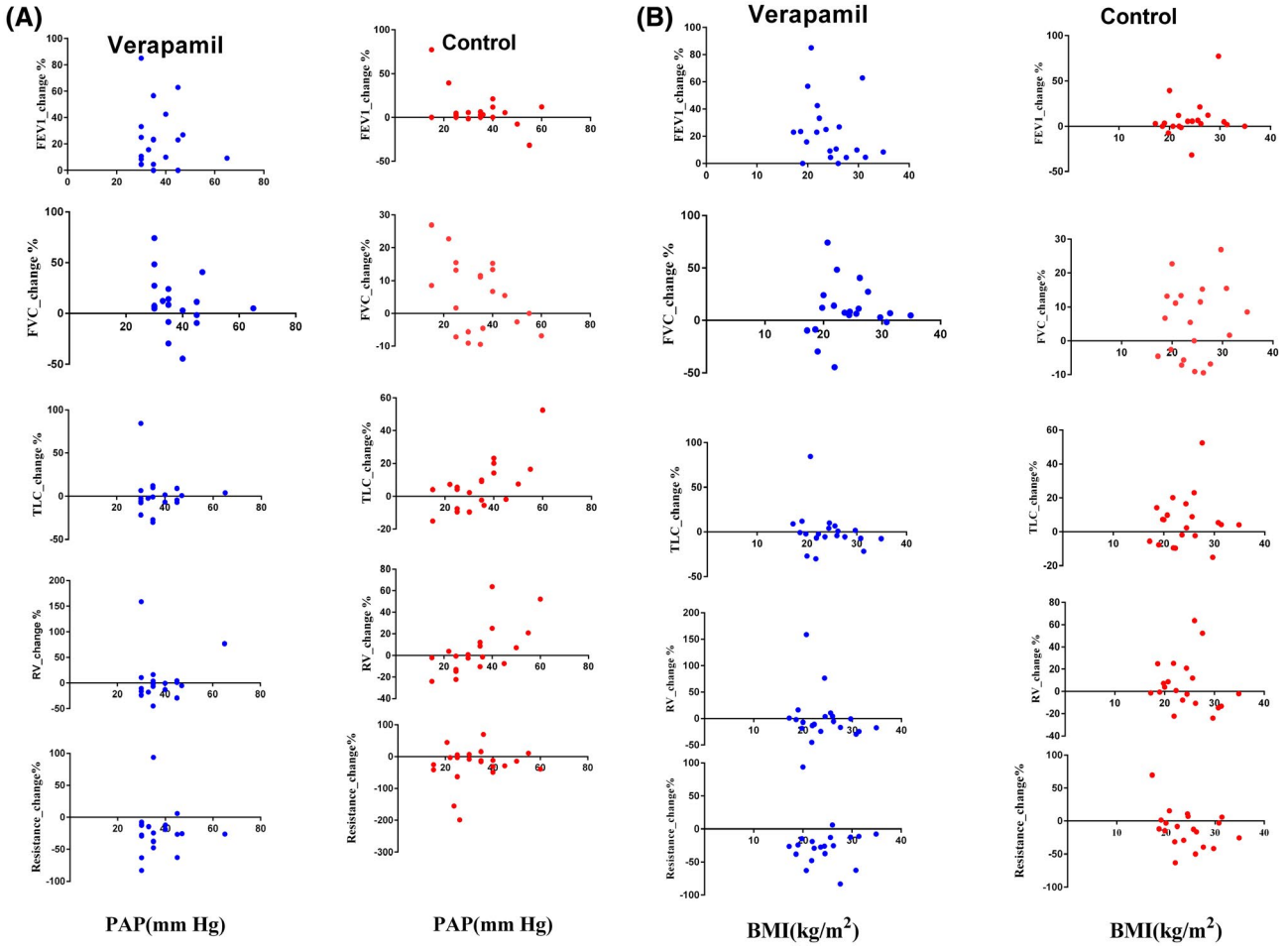

FIGURE 4 Correlation between change percentage of the study parameters and the PAP (A) and BMI (B). FEV1 change in the control group was affected by a rise in either PAP or BMI, while in the verapamil group, FEV1 change in the vertical axis despite rising in PAP or BMI, was considerable. BMI, body mass index, FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PAP, pulmonary artery pressure; RV, residual volume; TLC, total lung capacity

without the risk of cardiac effect or respiratory failure corresponding to diaphragm endurance.[29] However, in case of using an inhaled form of these agents, selective vasodilation is superior to systemic effect and dilation would occur in the well-ventilated region of the lung, correcting the ventilation-perfusion mismatch.[30]

In addition, the reducing effect of verapamil on the percentage of goblet cells and mucus secretion is another strong point conducing to its therapeutic effect on COPD patients.[31] Among smoker patients, the remarkable improvement in FEV1, FEV1/FVC and FEF 25-75 in verapamil compared with control group pointed out the strong bronchodilatory effect of CCBs. Indeed, in the control group, there was no difference among smokers regarding either of the three mentioned parameters. However, Calverley et al assessed salbutamol and ipratropium on 660 COPD patients and stated that smoking status was not related to bronchodilator response.[32]

This study had some limitations: patients received just one single dose of the drug, while continuous use may have revealed more positive effects or side effects. Although Bartolome et al emphasized that the long-term administration of bronchodilator (tiotropium) significantly improved TGV R, in our study, there was no change in TGV value and lung hyperinflation rate.

Also, pulmonary arterial pressure before and after the intervention was not measured, and the COPD-asthma overlap disorders were not excluded from the study.

From GOLD stage point of view, our study showed that the therapeutic effect was considerable in GOLD IV. The number of GOLD IV in verapamil group was lower than that of placebo. Therefore final output was not affected by GOLD stage.

5 | CONCLUSION

Despite such various risk factors as high BMI, age >60 years, high PAP, smoking impaired treatment outcomes,[27,33] it seems that inhaled verapamil acts as a multi-functional agent, although proper patient selection is crucial.

More research is needed to assess the effect of longer consumption of nebulized verapamil among COPD patients. Serial PAP measurement and walking tests are further recommended after excluding the subjects with asthma-COPD overlap syndrome.

CONFLICT OF INTEREST

This submission has not been published anywhere previously and is not simultaneously being considered for any other publication. The authors report no declaration of interests.

AUTHOR CONTRIBUTIONS

Rama Bozorgmehr, Maryam Edalatifard, Besharat Rahimi, Shahideh Amini, collected the data. Rama Bozorgmehr, Maryam Edalatifard, Enayat Safavi, Fariba Ghorbani, Hamidreza Abtahi and Guitti Pourdowlat analysed the data, all authors contributed in the interpretation of the data. All authors contributed in preparing of the first and final version of the study.

ETHICS

The study protocol was approved in the ethics committee of Imam Khomeini Hospital complex—Tehran University of Medical Sciences (code: IR.TUMS.IKHC.REC.1397.O89) and written informed consent form was obtained from patients.

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How to cite this article: Bozorgmehr R, Edalatifard M, Safavi E, et al. Therapeutic effects of nebulized verapamil on chronic obstructive pulmonary disease: A randomized and double-blind clinical trial. *Clin Respir J*. 2020;14:370–381. https://doi.org/10.1111/crj.13142