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ORIGINAL PAPER

The Effect of Sildenafil on Respiratory Weaning of Patients with Chronic Obstructive Pulmonary Diseases Admitted to Intensive Care Unit

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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a common disease that tends to occur worldwide and is a common cause of respiratory failure requiring mechanical ventilation and admission to the intensive care unit (ICU). The present study was carried out to investigate the efficacy of sildenafil in facilitating the weaning of COPD patients from the ventilator. **Methods:** This randomized double blind clinical trial study was carried out with 40 patients suffering from COPD. The patients were divided in two study groups. 20 patients belonging to Group I received 20 mg sildenafil tablets twice a day for one week while 20 patients of the second group (Group II) received placebo tablets with the same dosage. Respiratory parameters like rapid shallow breathing index (RSBI), mixed venous oxygen pressure (PvO2) and plateau pressure were measured in both groups. Data were analyzed on the basis of student's t – test and $\chi 2$ test using SPSS 16 software. **Results:** The results are expressed as mean ± SE and $P < 0.05$ is considered statistically significant. According to our findings RSBI was lower in Group I compared with Group II after one week of treatment (P= 0.032). PvO2 value was higher in sildenafil group compared with placebo group (P=0.025). Plateau pressure was lower in first group than group II (P=0.022). **Conclusion:** Sildenafil facilitated weaning of COPD patients from the ventilator by improving the respiratory parameters. **Key Words: Chronic Obstructive Pulmonary Disease (COPD), Sildenafil, respiratory weaning, Pulmonary hypertension, Intensive care unit (ICU).**

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1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is common cause of respiratory failure and admission to the intensive care unit (ICU) (1). COPD is one of the major causes of chronic morbidity and mortality throughout the world (2). Patients with COPD represent a large portion of those mechanically ventilated in the ICU (3). Mechanical ventilation of patients with COPD represents a unique set of challenges compared with other patients (1).

COPD is a disease state characterized by irreversible airflow limitation and dynamic pulmonary hyperinflation[2]. Physiologically, COPD represents a disruption in ventilation and gas exchange in the lungs[3]. Ventilatory intervention is often life-saving when patients with asthma or COPD experience acute respiratory compromise (4). Although both noninvasive and invasive ventilation methods may be viable initial choices, which depends upon the severity of illness, the rapidity of response, coexisting diseases and capacity of the medical environment. In addition, noninvasive ventilation often relieves dyspnea and hypoxemia in patients with severe COPD (4). Laboratory tests of COPD patients indicate elevated CO_2 level, gradual reduction of the levels of oxygen and pH in arterial blood and a consequent rise in the dead space fraction (DSF) of the lungs (3). Inhalation of nitric oxide (NO) dilates the pulmonary vasculature and enhances perfusion to ventilated lung regions, thereby improving oxygenation in patients with acute respiratory distress syndrome (ARDS) (5, 6). However, NO inhalation as an adjunctive therapy is controversial, since a considerable number of patients are unresponsive, and NO also has adverse effects, including renal dysfunction (7, 8). Pulmonary hypertension (PH) is a characteristic feature of acute respiratory distress syndrome (ARDS) and contributes to mortality (9). Also PH has been present in more than 50% of patients with severe COPD (10).

Sildenafil citrate (Revatio), an inhibitor of phosphodiesterase type 5 (PDE5) is approved for the treatment of pulmo-

nary arterial hypertension (PAH) (11). A family of enzymes called phosphodiesterases (PDE) inactivates cGMP by converting it to GMP (12). During sepsis, pulmonary cGMP release may be impaired, thereby accounting for the pulmonary vascular unresponsiveness to NO (13, 14).

Oral sildenafil and intravenous epoprostenol have independently been shown to be effective in patients with pulmonary arterial hypertension (14). Administration of sildenafil in ambulatory patients with pulmonary hypertension improves oxygenation and ameliorates pulmonary hypertension (9).

It has been demonstrated that sildenafil increases exercise capacity during severe hypoxia in healthy volunteers and improves gas exchange in patients with pulmonary hypertension by selectively dilating arteries in well ventilated areas of the lung (16, 17). Although some studies have reviewed the effect of sildenafil in ventilatory characteristics in non-intubated COPD patients (10, 18), respiratory weaning facilitation with sildenafil in COPD patients under mechanical ventilation has received little attention (19).

We carried out the present study in order to evaluate the efficacy of sildenafil in facilitating the weaning of COPD patients from the ventilator admitted in the ICU of Imam Reza Hospital from 2010-2011.

2. MATERIALS AND METHODS

This randomized double-blind, placebo-controlled study was carried out with forty patients suffering from COPD who were mechanically ventilated in ICU. The Institute's Ethics Committee approved this study (NO: 1024) and written informed consent was obtained from each participant. The patients were divided into two groups with the aid of a computer generated random number table. Data collector and patients were blinded to the study group assignment. Our inclusion criteria were being a COPD patient with class II disease stage according to classification of American Society of anesthesiologists (ASA). Patients who could not receive the drug through gavage due to digestive problems and patients who could not tolerate the drug, like those inducing low blood pressure (systolic blood pressure < 90 mm Hg) were excluded from the study.

All patients were ventilated by a Evita II (Drager medical, Germany) ventilator in ICU. Patients were mechanically ventilated with synchronized intermittent mandatory (SIMV) mode and a set of tidal volume (V_T) of 10 ml/kg, respiratory rate (RR) of 12 breath/min, F_IO_2 of 0.6, positive end expiratory pressure (PEEP) of 5 cm H_2O and a pressure support (PS) of 10 cm H_2O. According to the patients' respiratory conditions and to maintain their SpO_2 > 90% and PCO_2 = 35- 40 mm Hg ventilator setting was inspected throughout the study from time to time. Twenty patients belonging to Group I received 20 mg of sildenafil (Rouz Darou laboratories, Iran) tablets twice a day (every 12 hours) for one week while twenty patients in Group II received placebo tablets. Respiratory parameters like rapid shallow breathing index (RSBI), mixed venous oxygen pressure (PvO_2) and plateau pressure were measured in both groups. To calculate the RSBI, the ventilator was adjusted on spontaneous ventilation mode and the most frequent tidal volume and respiratory rate were recorded during one minute spontaneous ventilation. To calculate the plateau pressure while the patient was under mechanical ventilation and received a constant tidal volume, we used temporary 20-second expiratory occlusion maneuver and created a pause in the beginning of the next inspiration (Inspiratory pause). According to Fick's equation, the rate of PvO_2 is an index of cardiac output (Q_T), so oxygen pressure of venous blood (PvO_2) may be calculated by a sample of venous blood collected by central venous catheter.

Results were analyzed on the basis of Student's t test and χ^2 test using SPSS for windows software (version 16.0, SPSS Inc., Chicago, IL). The results are expressed as mean ± SE and $P < 0.05$ is considered statistically significant.

	Group I (sildenafil)	Group II (placebo)	*P* value
Age (yr)	48.8 ± 1.3	49.8 ± 1.4	NS*
Sex (men/women)	10/10	9/11	NS**
Weight (kg)	76.1 ± 1.17	75.7 ± 0.92	NS*
Height (Cm)	1.72 ± 0.01	1.71 ± 0.01	NS*
BMI (kg/m²)	26.9 ± 0.5	28.4 ± 0.7	NS*
Data are presented as mean ± standard error, or frequency. NS: not significant (P > 0.05), *t test, ** χ^2 test BMI: Body mass index			

Table 1. Demographic characteristics in the two study groups.

	Group I (sildenafil)	Group II (placebo)	*P* value*
Rapid Shallow Breathing Index (RSBI)	45.4 ± 3.9	50.8 ± 4.8	0.032
Mixed Venous Oxygen Pressure (PvO_2)	35.3 ± 1.34	29.3 ± 0.9	0.025
Plateau pressure (Cm H2O)	21 ± 2.5	24.7 ± 2	0.022
SpO2 (%)	95 ± 7.3	92 ± 8.4	0.081
PaCO2 (mm Hg)	42 ± 6.2	43 ± 6.4	0.133
Mechanical ventilation duration (hours)	82 ± 12	94 ± 14	0.042
ICU length of stay (days)	6.1 ± 0.6	7.2 ± 0.8	0.074
Data are presented as mean ± standard error. *t test			

Table 2. Respiratory characteristics in the two study groups during ICU stay.

3. RESULTS

In this clinical trial forty COPD patients under mechanical ventilation admitted to ICU were studied. Comparison of the demographic parameters of the two groups showed no significant differences between the two groups (Table 1). The RSBI was lower in Group I treated with sildenafil compared with Group II who received placebo after one week of treatment (Table 2). Also mean PvO_2 values were higher in sildenafil group compared with placebo group and plateau pressure was lower in Group I than that in group II (table 2). The average duration of mechanical ventilation was shorter in sildenafil group compared to the placebo group. The duration of ICU stay was not statistically different between two groups ($p > 0.05$) (Table 2).

4. DISCUSSION

Ventilatory intervention is often life-saving when patients with asthma or COPD experience acute respiratory compromise. It is crucial to provide

controlled hypoventilation, longer expiratory time and titrated extrinsic positive end-expiratory pressure to avoid its consequences (4). Sildenafil has a direct action on the pulmonary circulation, thereby improving pulmonary blood flow and more uniform ventilation–perfusion matching, reducing the ventilatory requirement for exercise. This improvement in pulmonary blood flow would be reflected by improved ventilation (VE) relative to CO2 output (V CO2), and by improved end-tidal carbon dioxide tension ($P_{ET}CO2$), both measured at the anaerobic threshold (AT). Recent advances have led to FDA approval of oral phosphodiesterase- 5 inhibitor sildenafil in treatment of pulmonary hypertension (20). Sildenafil may have resulted in general pulmonary vasodilation, increasing blood flow through both well ventilated as well as hypoventilated (consolidated) areas, thereby reducing hypoxic vasoconstriction and increasing the shunt fraction, which in turn resulted in a lower oxygenation (9).

According to study by Ronald et al. along with the improvement in pulmonary perfusion, both peak work rate and peak O2 pressure improves significantly with sildenafil (20). In the present study we also employed mechanical ventilation for our patients as a treatment strategy. This study is case specific; so it is a unique characteristic of this study that only COPD patients were considered. We showed that sildenafil improved weaning from the ventilator. The same finding is reported by other researchers (20, 21, 22). In the present study, we administered oral sildenafil 20 mg twice daily while Croom & Curran in their study gave their patients 20 mg oral sildenafil three times daily (11). Stanopoulos et al administered 50 mg of sildenafil through the nasogastric tube (19). Sildenafil may cause side effects like decrease in blood pressure as is stated by Cornet et al. They showed that mean arterial pressure (MAP) decreased markedly after 50 mg of sildenafil together with a reduced systemic vascular resistance (SVR) (9). That is why we used the lowest dose of sildenafil i.e. 20 mg twice daily.

We measured certain respiratory parameters like RSBI, PvO_2 and plateau pressure to evaluate the efficacy of sildenafil on weaning of patients from ventilator. For this purpose we used the blood collected from central venous catheter that used for patients hemodynamic monitoring (CVP) and no new needle puncture was needed for collecting blood. Ronald et al. demonstrated that brief treatment with sildenafil resulted in improvement of ventilator efficiency (20). Yamanaka and colleagues showed that usage of sildenafil reduced the difference between arterial carbon dioxide pressure and expiratory carbon dioxide pressure ($PaCO2–P_{ET}CO2$), which indicates a reduction in physiological dead space (VD / VT) (22).

On the other hand, in a study conducted by Charan the bronchodilator effects were attributed to the sildenafil (23). In our study it was found that in COPD patients due to auto-PEEP and hyper dynamics aeration (Alveolar vessel compression = dynamic hyperinflation) created during the weaning, have been a reduced tidal volume and increased alveolar pressure (plateau) therefore sildenafil usage can reduce alveolar pressure and increase RSBI in patients due to bronchodilator effect of sildenafil through inhibiting the phosphodiesterase-5 enzyme, and thereby increase cGMP that the increase in pulmonary perfusion, especially in areas with a ratio of V / Q mismatch (19). It may be concluded from the present study that sildenafil by improving the respiratory parameters like PvO_2 value, RSBI and plateau pressure, facilitates weaning of COPD patients from the ventilator.

Conflict of interest: none declared.

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