Original Article

EFFECTS OF PROGESTERONE ON THE VENTILATORY PERFORMANCE IN ADULT TRAUMA PATIENTS DURING PARTIAL SUPPORT MECHANICAL VENTILATION

Mohammad Golparvar MD, Farzad Ahmadi MD, Mahmood Saghaei MD•

Background: Previous studies have shown that progesterone increases the ventilatory performance in healthy individuals and in patients with chronic obstructive pulmonary disorders. The study was designed to investigate the effect of a single intramuscular administration of progesterone on ventilatory performance in adult trauma patients during partial support mechanical ventilation.

Methods: Forty adult trauma patients undergoing partial support mechanical ventilation with a spontaneous minute ventilation of 30 – 50% of their total minute ventilation were randomly given a single intramuscular injection of either progesterone 1 mg/kg or normal saline as placebo. Airway resistance and pressure, lung compliance, spontaneous tidal volume and respiratory rate, pulse oxymetric oxygen saturation, end tidal CO_2 concentration, heart rate, and blood pressure were measured and compared between two groups before administration of progesterone (or placebo) and three and six hours after it.

Results: Three hours after progesterone administration maximum negative inspiratory pressure, spontaneous tidal volume, dynamic compliance, and oxygen saturation were increased while peak airway pressure, airway resistance, and end tidal CO_2 concentration decreased significantly compared to the basal values and those in the placebo group. These changes returned to baseline between three to six hours after progesterone administration.

Conclusion: The results of this study show the beneficial effect of a single intramuscular administration of progesterone on the ventilatory performance during partial support mechanical ventilation, which lasts for three to six hours. Whether more frequent administration of progesterone is of value for the management of mechanical ventilation and in particular the weaning process, remains to be elucidated in future studies.

Archives of Iranian Medicine, Volume 8, Number 1, 2005: 27 – 31.

Keywords: Mechanical ventilation • progesterone • respiratory drive • ventilatory performance • weaning process

Introduction

Despite the innovation of new protocols for mechanical ventilation, many aspects of patient management, specially their weaning processes still present dilemmas to the respiratory care physician.[1] Different drugs and techniques have been attempted to increase the ventilatory performance and counteract muscle dysfunction due to the prolonged periods of mechanical ventilation, and an increased contribution of the patient in the total minute ventilation.[2] Pharmacological optimization of the respiratory control mechanism has been shown in infants to be associated with substantial improvement in pulmonary function.[3] Progesterone, by increasing the ventilatory performance, has been shown to increase the ventilatory capacity and exercise performance in normal subjects.[4 – 7] In obstructive airway diseases, this drug has led to an improvement in ventilatory control and pulmonary gas exchange.[8, 9] In addition, previous studies on postmenopausal women with respiratory insufficiency or partial

Authors affiliation: Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran.
•**Corresponding author and reprints:** Mahmood Saghaei, MD, Department of Anesthesia, Al-Zahra Medical Center, Isfahan, Iran. P. O. Box: 931, Fax: +98-311-2263193,
E-mail: saghaei@med.mui.ac.ir.

upper airway obstruction have confirmed the effectiveness of medroxyprogestrone in restoring the patency of their upper airway and respiratory control mechanism.[10, 11] Although the majority of previous studies have shown some beneficial effects of progesterone on ventilatory performance, no study has been performed to evaluate its effectiveness in patients under mechanical ventilation. Patients on mechanical ventilation may have different cardiorespiratory functions and a different response to progesterone therapy. A major problem in clinical management of these patients is the weaning process, during which partial support mechanical ventilation is used together with different drugs and techniques to facilitate the weaning process. Since the effect of progesterone on the ventilatory performance during partial support mechanical ventilation has not been defined in previous studies, the present study was designed to investigate the effect of a single intramuscular administration of progesterone on the ventilatory performance in adult trauma patients during partial support mechanical ventilation.

Patients and Methods

This study was a randomized, double bind, placebo controlled clinical trial. Location of this study was a university hospital intensive care unit.

After institutional ethics committee approval and informed written consent from patients' relatives, forty adult trauma patients undergoing partial support mechanical ventilation with stable cardiorespiratory function (as defined in the exclusion criteria), were prospectively studied. These patients were admitted to the intensive care unit after surgical procedures for multiple trauma. Surgical operations were emergency laparotomy (26 cases), vascular procedure needing massive transfusion (10 cases), and lower limb amputation in 8 cases (including 4 cases of vascular procedures).

Patients were included in the study if their spontaneous minute ventilation were between 30 and 50% of their total minute ventilation, and the ventilator mode was synchronous intermittent mandatory ventilation (SIMV) plus pressure support ventilation (PSV). Exclusion criteria were: history of chronic obstructive pulmonary diseases, history of severe cardiovascular disorder, peak airway pressure (P_{peak}) > 30 cmH_2O, positive end-expiratory pressure > 7 cmH_2O, systolic arterial blood pressure < 90 mmHg or > 160 mmHg, heart rate < 60/min or > 120/min, axillary temperature > 37.5 or < 36.5°C, body weight > 90 kg, duration of mechanical ventilation > 7 days or < 3 days, level of pressure support > 10 cmH_2O, infiltration in chest X-ray more than one quadrant, lung contusion after trauma, airway secretion needing suctioning sooner than every 30 minutes, abdominal distension, PaO_2/FiO_2 ratio < 270, ventilator mode change during the past 24 hours, any contraindication to progesterone administration, patients already on progesterone, patients receiving aminophylline or muscle relaxant, and patients needing vasoactive drugs.

Regardless of patient's ventilator mode, during the study period the ventilator mode was a low-rate SIMV plus PSV (7,200 Series Microprocessor Ventilator, Puritan-Bennett Corporation, Carlsbad, CA) with the same settings for all patients (Table 1). Patients received 3 mg of intravenous midazolam at the start of the study and 1 mg/hr as a continuous infusion thereafter.

The low rate of mandatory or assisted breaths was selected to facilitate tracing the changes in ventilatory performance. Most of other settings (e.g. PSV = 10 cmH_2O) were selected in such a way to maximize the inclusion of patients into the study without violating ethical concepts (e.g. exposing the patient to a PSV less than what he/she is receiving).

With the aid of a computer-generated list of 40 (2 × 20) shuffled allocations (Random Allocation Software, M. Saghaei, Isfahan, Iran), patients were randomly given a single intramuscular injection of either progesterone (1 mg/kg) or normal saline as the placebo. Patients group remained obscure until the completion of the study, when data of all patients entered into the computer.

Table 1. Ventilator parameter settings used during the study period.

Ventilatory parameter	Settings
Mode	SIMV [a] + PSV [b]
Respiratory rate (BPM)	4
Tidal volume (mL/kg)	10
FiO_2	0.45
Plateau time (sec)	0.6
Inspiratory flow waveform	Constant (square wave)
Inspiratory flow rate (LPM/kg)	0.8
PEEP/CPAP (cmH_2O)	5
Pressure support (cmH_2O)	10
Triggering mode	Flow
Value (sense: base, LPM)	3: 5

SIMV [a] = synchronous intermittent mandatory ventilation; PSV [b] = pressure support ventilation; PEEP/CPAP = positive end-expiratory pressure/continuous positive airway pressure.

Thirty minutes after placing the patient on the new ventilatory settings, different ventilatory variables together with heart rate and blood pressure were measured and immediately after it, intramuscular administration of progesterone or placebo was performed. Three and six hours after administration of progesterone (or placebo) the measurements were repeated. The three hours time interval between measurements was selected to allow for the peak effect of intramuscular progesterone to occur.[12] Blood pressure was measured with automated noninvasive method (Datex Cardiocap II; Datex/Division of Instrumentarium Corp., Helsinki, Finland). After completion of the study, patients were returned to their previous ventilatory settings.

To evaluate the ventilatory performance, following data were recorded:

- Data corresponding to mandatory/assisted breaths: P_{peak}, mean airway pressure (P_{mean}), plateau pressure (P_{plat}), static and dynamic compliances (C_s, C_d), and airway resistance (R_A).
- Data corresponding to patient's spontaneous respiratory activity: maximum negative inspiratory pressure (NIP_{max}), spontaneous tidal volume (VT_{sp}), and spontaneous respiratory rate (RR_{sp}).

The data for spontaneous respiratory activity were measured fifteen minutes after recording the data of mandatory/assisted breaths.

During these measurements no instruction was given to the patient to change his/her ongoing pattern of ventilatory efforts. These ventilatory data were measured with the monitoring module of the ventilator (7,200 Series Microprocessor Ventilator). In addition, pulse oxymetric oxygen saturation (SpO_2) and end tidal CO_2 concentration ($ETCO_2$) were measured (Datex Cardiocap II). During the study period if there was a need to change the ventilator settings (e.g. patient did not tolerate the new settings) the case was excluded from the study. Measurements were performed and recorded by an anesthesiologist who was unaware of the patient group. All measurements were recorded as the mean of three consecutive measurements with a twenty-second interval between measurements. Final outcomes of patients defined as dead or discharged and total duration of mechanical ventilation in discharged patients were recorded.

Data were presented as mean ± SD. Mann-Whitney U test was used to compare quantitative variables between the two groups. Nominal data were compared with the Fisher exact test. A value for $P < 0.05$ was considered as statistically significant. Statistical analysis was performed on a computer using SPSS 10.0 software.

Results

A total of 53 patients were selected for the study. Eight patients in placebo group and five patients in progesterone group were excluded from

Table 2. Demographic and ventilatory characteristics of patients (data are mean ± SD or *n* (%) where appropriate).

	Placebo	**Progesterone**
Age (year)	42 ± 17	42.6 ± 19
Weight (kg)	67.6 ± 15	68 ± 12
Sex		
Female	4 (20)	5 (25)
Male	16 (80)	15 (75)
Airway		
Tracheal tube	14 (70)	15 (75)
Tracheostomy	6 (30)	5 (25)
Days of mechanical ventilation	8.8 ± 2	9.2 ± 3
Respiratory rate (BPM)		
Spontaneous	11 ± 5	12 ± 5
Controlled	5.8 ± 1	5.9 ± 1.1
Tidal volume (mL)		
Spontaneous	131 ± 61	134 ± 73
Controlled	410 ± 80	425 ± 90
FiO_2	0.44 ± 0.01	0.45 ± 0.015
PEEP/CPAP (cmH_2O)	6.2 ± 2	6.8 ± 2.5
Pressure support (cmH_2O)	7 ± 2.7	6 ± 3
Modified lung injury score (0 – 20) [a]	5.1 ± 0.4	5.3 ± 0.5

[a] As described by Offner et al[13]; No significant differences between the two groups; PEEP/CPAP = positive end-expiratory pressure/continuous positive airway pressure.

the study because they needed some modification in ventilator settings during the study period. Therefore, final analysis was performed on the remaining forty patients (twenty in each group).

The groups were comparable with respect to basal characteristics and ventilatory data (Table 2). At three hours after progesterone administration NIP_{max}, VT_{sp}, C_d, and SpO_2 increased while P_{peak}, R_A, and $ETCO_2$ decreased significantly compared to the basal values and those in the placebo group (Figure 1). Two groups were not significantly different with respect to changes in blood pressure and heart rate (Figure 2). The changes in variables recorded at six hours after progesterone administration were not significantly different

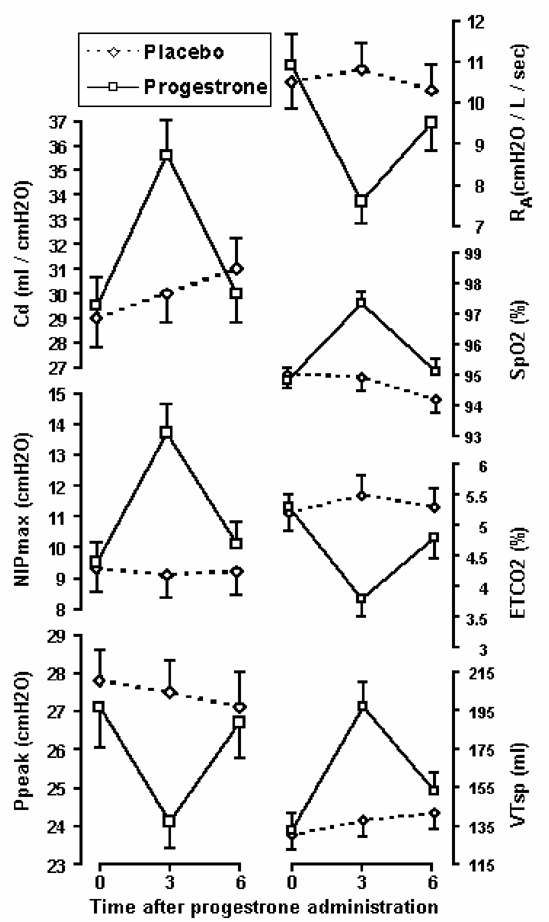

Figure 1. Variables with significant changes at 3 hours after progesterone administration (data points are mean with their standard error [SE]. P_{peak} = peak airway pressure; C_d = dynamic compliance; R_A = airway resistance; NIP_{max} = maximum negative inspiratory pressure; VT_{sp} = spontaneous tidal volume; $ETCO_2$ = end tidal CO_2; andSpO_2 = pulse oxymetric saturation).

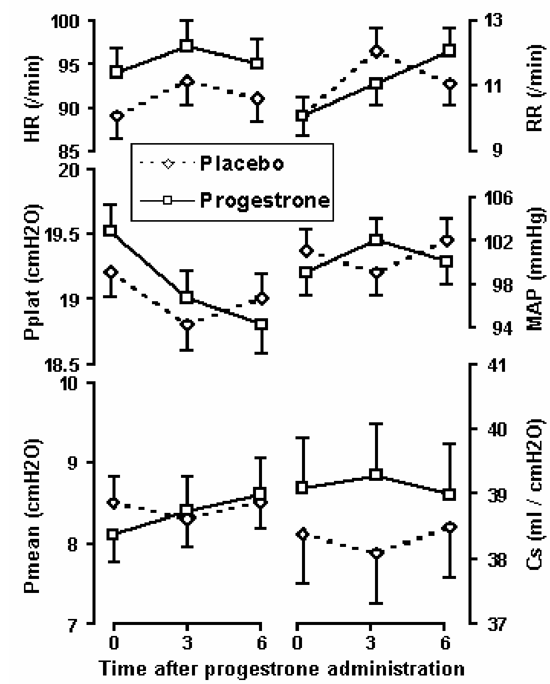

Figure 2. Variables with insignificant changes after progesterone administration (data points are mean with their standard error [SE]. P_{mean} = mean airway pressure; P_{plat} = plateau pressure; Cs = static compliance; RR_{sp} = spontaneous respiratory rate; MAP = mean arterial pressure; and HR = heart rate).

compared to the basal value and those in the placebo group (Figures 1 and 2). Duration of mechanical ventilation and the frequencies of live discharges were not significantly different between the two groups (Table 3).

Discussion

The results of this study show that a single intramuscular administration of progesterone increases the ventilatory performance in adult trauma patients during partial support mechanical ventilation. This effect, which lasts for three hours, is evident from the significant increases in NIP_{max} and VT_{sp} at three hours following intramuscular progesterone administration. In addition, an increase in SpO_2 and a decrease in $ETCO_2$ further support this hypothesis. The increase in ventilatory performance after progesterone administration in the present study is in accordance with a previous study on normal subjects and also in menopausal women with respiratory insufficiency.[5, 7] Progesterone has been used in chronic obstructive lung diseases to enhance the ventilatory

Table 3. Duration of mechanical ventilation and the frequencies of live discharges (data are mean ± SD or n [%]).

		Placebo	Progesterone
Days of mechanical ventilation[a]	Total	17.3 ± 4	16.9 ± 3
	After study	8.5 ± 3	7.7 ± 2
Outcome	Survived	18 (90)	19 (95)
	Dead	2 (10)	1 (5)

[a] In survivors; No significant differences between two groups.

performance and to improve the gas exchange.[8, 9] In postmenopausal females, this drug has been used to overcome the partial upper airway obstruction during sleep.[11] Whether these effects on ventilatory performance is a nonspecific action on central nervous system (CNS) or a rather specific mechanism at the level of respiratory center, remains to be clarified. In addition, progesterone may have a local pulmonary effect, which results in bronchodilatation and improvement in gas exchange.[10, 11]

Although increases in ventilatory performance following a single intramuscular administration of progesterone is not adequate to facilitate weaning process, the main objective of this study was to demonstrate its acute effect on ventilatory performance. Further researches are needed to first evaluate the role of the different components of ventilatory performance (i.e. respiratory drive, respiratory muscles activity, airway resistance, and pulmonary gas exchange) in weaning process and then to try more frequent dosing of progesterone, specially during and immediately after weaning.

In conclusion, the results of this study show that a single intramuscular administration of progesterone can increase the ventilatory performance during partial support mechanical ventilation. In cases of ventilator dependency due to impaired ventilatory performance, increasing some components of the ventilatory performance (e.g. respiratory drive) would facilitate the weaning process. Whether more frequent administration of progesterone or uses of agents with longer duration of action is of value for the management of mechanical ventilation and specially to help the patients to wean successfully from mechanical ventilation, remains to be elucidated in future studies.

References

1. Ely EW. The utility of weaning protocols to expedite liberation from mechanical ventilation. *Respir Care Clin N Am*. 2000; **6:** 303 – 319.
2. Chao DC, Scheinhorn DJ. Weaning from mechanical ventilation. *Crit Care Clin*. 1998; **14:** 799 – 817.
3. Locke RG, Salvia JV. Pharmacologic manipulation of the respiratory control center in the infant. *J Am Osteopath Assoc*. 1990; **90:** 602 – 612.
4. Bonekat HW, Dombovy ML, Staats BA. Progesterone-induced changes in exercise performance and ventilatory response. *Med Sci Sports Exerc*. 1987; **19:** 118 – 123.
5. Dombovy ML, Bonekat HW, Williams TJ, Staats BA. Exercise performance and ventilatory response in the menstrual cycle. *Med Sci Sports Exerc*. 1987; **19:** 111 – 117.
6. Robertson HT, Schoene RB, Pierson DJ. Augmentation of exercise ventilation by medroxyprogesterone acetate. *Clin Physiol*. 1982; **2:** 269 – 276.
7. Mikami M, Tatsumi K, Kimura H, Honda Y, Kuriyama T. Respiration effect of synthetic progestin in small doses in normal men. *Chest*. 1989; **96:** 1073 – 1075.
8. Delaunois L, Delwiche JP, Lulling J. Effect of medroxyprogesterone on ventilatory control and pulmonary gas exchange in chronic obstructive patients. *Respiration*. 1985; **47:** 107 – 113.
9. Morrison DA, Goldman AL. Oral progesterone treatment in chronic obstructive lung disease: failure of voluntary hyperventilation to predict response. *Thorax*. 1986; **41:** 616 – 619.
10. Saaresranta T, Polo-Kantola P, Irjala K, Helenius H, Polo O. Respiratory insufficiency in postmenopausal women: sustained improvement of gas exchange with short-term medroxyprogesterone acetate. *Chest*. 1999; **115:** 1581 – 1587.
11. Saaresranta T, Polo-Kantola P, Rauhala E, Polo O. Medroxyprogesterone in postmenopausal females with partial upper airway obstruction during sleep. *Eur Respir J*. 2001; **18:** 989 – 995
12. Gonzales NM. Hormones. In: White PF, ed. *White Anesthesia Drug Manual*. Philadelphia: WB Saunders; 1996: 243 – 244
13. Offner PJ, Moore EE. Lung injury severity scoring in the era of lung protective mechanical ventilation: the PaO_2/FiO_2 ratio. *J Trauma*. 2003; **55:** 285 – 289