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Original Article

Effect of Nebulized Eucalyptus on Arterial Blood Gases and Physiologic Indexes of Mechanical Ventilated Patients: A Randomized Clinical Trial

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Abstract

Introduction: Arterial hypoxia is one of the most common findings in critically ill patients. Inhaled medications in ventilated patients can reduce airway resistance, facilitate dilution, and prevent airway infections. This study aimed to examine the effects of nebulized Eucalyptus (NE) on arterial blood gases (ABG) and physiologic indexes of patients receiving mechanical ventilation (MV).

Methods: The current randomized clinical trial was performed in three intensive care units (ICUs) of Al-Zahra Hospital in Isfahan, Iran. Using purposive sampling method, 70 intubated patients were selected and randomly divided into NE (n=35) and control (n=35) groups. NE group received 4 ml (5%) Eucalyptus in 6 mL normal saline (NS) every 8 hours since intubation to 3 days by a nebulizer. Control group received 10 mL NS in the same way. Glasgow Coma Scale (GCS) and ABG parameters (pH, BE, HCO3, PCO2, SaO2, and PaO2), and the peak inspiratory pressure (PIP) and tidal volume (TV) were equally assessed in both intervention and control groups. Data were analyzed using SPSS software version 13.

Results: There was no significant difference between the patients of both groups in terms of vital signs (blood pressure, temperature, respiratory rate, and pulse rate), GCS, pH, BE, HCO3, PCO2, SaO2, PaO2, PIP, and TV before the study. Amongst the parameters of ABG, there was a significant difference between PaO2 and SaO2 and PIP in the intervention and control groups 3 days after intervention.

Conclusion: Inhaled Eucalyptus can improve oxygenation and reduce airway pressure in patients undergoing MV.

Introduction

Mechanical ventilation (MV) is essential for critically ill patients[1]; it improves gas exchange both in alveoli and tissue surfaces by facilitating inhalation and exhalation.[2] Since about 40%-65% of the patients hospitalized in the intensive care unit (ICU) require MV, it is regarded as one of the most common reasons for hospitalization in ICUs.[3] Bradypnea, lung injuries, acute respiratory distress syndrome (ARDS), tachypnea, changes in arterial blood gases (ABG), respiratory fatigue, neuromuscular disorders, and changes in consciousness level are the most important reasons for MV use in these patients.[4] Although MV is a vital part of saving critical ill patients, the use of this method is also associated with complications.[5] Hence, one of the most important aspects of care in these patients is airway care, prevention of its complications, and continuous monitoring of oxygenation quality.[6] Regardless of underlying diseases, several factors may impair oxygenation in these patients. Reduced lung compliance that usually occurs due to alveolar disorders such as pneumonia and ARDS, as well as increased airway resistance that usually occurs due to bronchospasm or lesions of upper airways are the main factors of oxygen delivery disorder.[7] Therefore, monitoring and attention to the quality and amount of oxygenation is one of the most important aspects of care in these patients, which is usually carried out by ABG analysis.[8]

ABG provides useful information about ventilation, oxygenation, and acid-base balance status in patients.[9] Changes in oxygenation, evaluation of presence or absence of hypoxia, and reduction in arterial oxygen levels are usually obtained by measuring PaO2 and oxyhemoglobin saturation (SaO2), which indicate the patient's clinical states and prognosis of respiratory status. Arterial hypoxia is one of the most common findings in the critically ill patients.[10]

Although MV can maintain oxygenation in these patients, it is necessary to use different methods for

improving oxygenation. For instance, it has been shown that prone position with positive end-expiratory pressure in patients with ARDS can improve ratio of ventilation to perfusion and oxygenation in patients undergoing MV.[11,12] Furthermore, use of alveolar recruitment maneuver improves oxygenation in patients with acute respiratory failure undergoing pressure support ventilation.[13-15] Use of nitric oxide, that improves blood circulation in the areas where ventilation is low by pulmonary vascular dilation, can reduce pulmonary shunt and improve oxygenation by reducing pulmonary vascular resistance.[16-18] Inhaled bronchodilators relax airway smooth muscles leading to improved outcomes and quality of life for patients with chronic obstructive pulmonary disease (COPD) such as dyspnea.[19] A study by de Lima Gondim et al showed that cineole (main ingredient of Eucalyptus) could be used as an adjunct to anti-inflammatory drugs in patients with asthma and COPD.[20] Sudhoff et al investigated the effect of cineole on excessive mucus secretion in an experimental model of rhino sinusitis in vitro, and for the first time, a significant reduction in the number of goblet cells (mucus secretion) was achieved.[21] Also, a study by Worth and Dethlefsen showed that patients who received cineole had an increased forced expiratory volume than those who received a placebo, which could improve oxygenation.[22] The results of a study by Fischer and Dethlefsen in COPD patients showed that cineole reduced the severity of the disease and improved lung function, respiratory symptoms, and quality of life scores during six months.[23] Changes in the airway microbiome with bacteria and viruses can lead to inflammation and exacerbation of the airways. Amini et al studies showed that nebulized Eucalyptus (NE) reduces bacterial biofilm in the trachea of patients under MV and reduces ventilator associated pneumonia.[24,25]

One of the treatments in mechanically ventilated patients is using inhaled medications that can reduce airway resistance, facilitate dilution, and prevent or treat airway infections.[26,27] On the other hand, using inhaled methods causes the drugs to directly, and in a therapeutic way, reach into airways and prevents drug systemic side effects.[28] In terms of the prevention and treatment of diseases, medicinal plants play an important role. In recent years, due to the importance of medicinal plants, extensive research has been carried out on the extraction of active products of medicinal plants. The beneficial effects of these plants, cheap and low cost, and environmental compatibility are among the reasons for using these medicinal plants.[29]

One of the medicinal plants used to improve respiratory state is Eucalyptus, which is used as an inhaler in complementary medicine. Eucalyptus has antibacterial, antiviral, and antifungal properties.[30] It has effective impacts against cold, flu, and other respiratory infections, including rhinorrhea and sinusitis. Inhalation of a few drops of Eucalyptus through nebulizer is a safe method, and it has a long history.[23] Cineole, as the main ingredient of Eucalyptus, is exclusively used in inflammatory airway diseases. As a mucolytic agent, it has a positive effect on activity of mucus tarsus to clear mucus, as well as bronchodilator and anti-inflammatory effects.[20,21,31]

Oxygenation disorders and increased airway resistance in mechanically ventilated patients have created incentives for use of new therapies such as inhaled medicine. Due to the anti-inflammatory and bronchodilator properties of Eucalyptus and its safety, and since no inhaled herbal medicines have been used for this purpose in mechanically ventilated patients, it might improve oxygenation and hemodynamic status of patients. Accordingly, this clinical trial aimed to investigate the effect of NE on ABG and physiological indexes of mechanically ventilated patients.

Materials and Methods

The current randomized single-blind clinical trial study was conducted in three ICUs (trauma, internal, and surgical) of Al-Zahra Hospital in Isfahan, Iran from August to November 2014. A total of 70 patients (age range: 18-65 years) with oral endotracheal tube (ETT), under at least 72 hours of medical ventilation and lack of pneumonia according to MCPIS-based lung infection (modified Clinical Pulmonary Infection Score), sensitivity to herbal compounds, sepsis, pulmonary thromboembolism, atelectasis, inflammatory diseases of gastrointestinal tract, biliary tract and severe liver diseases according to diagnosis of specialized physician (based on physical examination and observation of patient's companion) participated in the study. Patients who were transferred from the ward for any reason, had sudden changes in hemodynamic status, or had complications such as hives, itching, and cutaneous rashes due to their allergy to Eucalyptus were excluded from the study.

According to previous study,[21] sample size was estimated considering the error of the first (0.05 alpha), second type (0.20 beta), $P_1 = 0.07$, $P_2 = 0.5$ and the formula for comparing two ratios and the probability of dropping 20%. Once the patients were selected, they were randomly assigned into two equal groups of intervention (n = 35) and control (n = 35). For randomization, a coin was tossed for each participant to allocate to the intervention group or the control group. Consequently, the participants were same in the intervention and the control groups. The demographic information and baseline characteristics (cause of hospitalization, invasive interventions, history of chronic diseases, cause of endotracheal extubation, number of antibiotics intake, duration of intubation etc.) were recorded in the beginning of the study. All the patients received standard treatments and cares in accordance with their disease and based on physician's order. Both groups received oral care (oral toothbrush, mouthwash and normal saline, and secretion suction), chest physiotherapy, and position change in the same way. Following the prescription of an anesthetist, the

patients of the intervention group received 4 mL of Eucalyptus solution 5% along with 6 mL of normal saline 0.9% for 20-30 minutes every 8 hours since intubation to 3 days using a standard nebulizer system.[21] A standard nebulizer was used for all patients. In order to prevent re-inhalation of the exhaled air, some filters were put on the forced expiratory circuit. These filters consist of several layers that have antibacterial and antiviral action, as well as a hydrophobic layer that does not allow water and vapor to pass and prevent re-inhalation. The patients of the control group received the same treatment with only 10 mL of nebulized normal saline. Regarding the number of wards and nurses who took care of the patients, some trained researchers and a written protocol were used for unification of the methodology. Due to the presence of different patients and ICUs, the subjects were selected with the same proportion from each ward. Eucalyptus or placebo prescriptive (similar to the appearance of Eucalyptus incense solution) was performed in the morning and evening shifts by the researcher and in the night shift by the researcher's colleagues and for all patients in the same way. The position of all patients was supine. All patients were under synchronized intermittent mandatory ventilation mode with Drager mechanical ventilation device.

Data collection tool consisted of two sections including a demographic information questionnaire and a checklist to record the vital signs (diastolic blood pressure, systolic blood pressure, body temperature, pulse rate, and respiratory rate). The benchmark was Glasgow Coma Scale (GCS) and ABG analysis with AVL 993 Blood Gas device made in London. Cardio set x-110 IEI was used to measure the vital signs, which were calibrated by the technician every week. The vital signs were measured and recorded every hour and its daily mean was intended. GCS and ABG (BE, HCO3, PCO2, SaO2, and PO2) in the patient record, and the peak inspiratory pressure (PIP) and TV in ventilator were equally assessed in both intervention and control groups daily for up to 3 days. The variables were recorded by the main project researcher. The data obtained from the study tool were analyzed in SPSS software version 13 (SPSS Inc., Chicago, Ill., USA) after being encoded. Kolmogorov–Smirnov was used for determine normal distribution. Repeated Measures ANOVA (Analysis of Variance) and independent *t* test and chi-square were used. The significance level of $P< 0.05$ was intended for all the tests. Figure 1 shows CONSORT diagram.

Results

Out of a total of 90 initial patients, 20 patients were excluded due to not meeting the inclusion criteria. Of the 47 patients in the intervention group, 12 patients were excluded (five patients due to lack of observance of the protocol; one patient due to the prolonged duration of intubation for more than 14 days; two patients due to the contamination of ETT because of incorrect transference to the sterile cover; two patients due to positive blood culture; and two patients due to the risk of side effects). Of the 43 patients in the control group, eight patients were excluded (four patients due to lack of observance of the protocol; two patients due to the prolonged duration of intubation for more than 14 days; one patient due to contamination of the ETT because of incorrect transference to the sterile cover; and one patient due to positive blood culture). Finally, 70 patients (35 in each group) were included in the study.

Since the allocation of the subjects to groups was performed randomly, the two groups were compared in terms of demographic and baseline characteristics (Table 1). The results showed that there was no significant difference between the two groups in terms of gender, age, and the cause of hospitalization. Moreover, no significant differences were observed between the groups in terms of invasive interventions such as central venous catheter, chest tube, abdominal drainage, brain drainage, and catheter for hemodialysis. There was also no significant difference between the two groups in terms of endotracheal extubation, duration of intubation, antibiotics use, and bronchodilator drugs. There were no differences between the groups in terms of diabetes and COPD (Table 1).

To investigate the difference between the two groups in terms of qualitative variables, such as gender, cause of hospitalization in medical and surgery ICU, invasive interventions, cause of ETT removal, and type of underlying disease, chi-square and Fisher's exact tests were used. To investigate the difference between the two groups regarding quantitative variables, including age, duration of intubation, the amount of antibiotics and bronchodilators, independent *t* test was used.

There was no significant difference between the patients of both groups in terms of vital signs (blood pressure, body temperature, respiratory rate, and pulse rate), GCS, and ABG (pH, BE, HCO3, PCO2, SaO2, and PaO2), and PIP and TV before the study (Tables 2 and 3). Amongst the parameters of ABG, there was a significant difference between PaO2, SaO2, and PIP in the intervention and control groups in the third day after intervention (Table 3). There was no significant difference between PaCO2 and HCO3 of intervention and control groups in the third day after intervention (Table 2).

Discussion

This study aimed to determine the effect of NE on ABG and physiologic indexes of patients undergoing MV. Results showed that NE improved arterial oxygen (PaO2 index) and oxygen hemoglobin saturation (SaO2 index) in the patients undergoing MV. However, there was no significant changes in Paco2 or other ABG variables. The increase of the PaO2 in patients who received inhaled Eucalyptus was associated with reduced PIP, which was statistically significant. Although the effect of inhaled

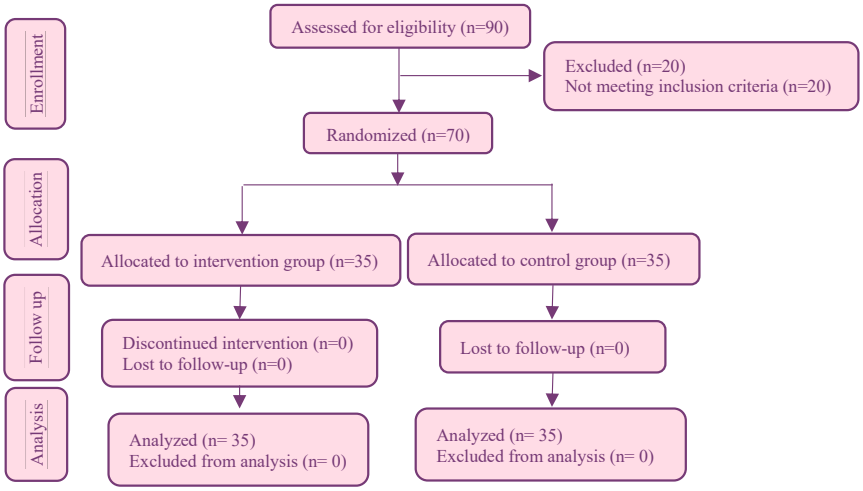

Figure 1. Flowchart of the study

Table 1. Patient characteristics in two intervention and control groups

Variable	Intervention group	Control group	*P* value[a]
	N (%)	N (%)	
Gender			
Male	27 (77.1)	26 (74.3)	0.78
Female	8 (22.9)	9 (25.7)	
Cause of hospitalization			
Multiple trauma	16 (54.7)	13 (37.1)	
Post-operative	9 (25.7)	15 (42.9)	0.31
Medical	10 (28.6)	7 (20)	
Invasive interventions			
CV line	9 (25.7)	13 (37.1)	0.30
Chest tube	2 (5.7)	5 (14.3)	0.23
Abdominal drain	1 (2.9)	5 (14.3)	0.19
Brain drain	14 (40)	10 (28.6)	0.31
Hemodialysis catheter	3 (8.6)	3 (8.6)	1
Cause of tracheal tube removal			
Improvement	20 (5.1)	18 (54.1)	
Death	13 (37.1)	12 (34.3)	0.47
Tracheostomy	2 (5.7)	5 (14.3)	
Underlying disease			
Diabetes	4 (11.4)	4 (11.4)	1
COPD	2 (5.7)	2 (5.7)	
Age[c]	48.9 (17.17)	54.2 (13.99)	0.16[b]
Duration of intubation[c]	6.11 (3.16)	6.66 (3.62)	0.50[b]
Antibiotics drugs[c]	1.83 (1.07)	2.03 (0.92)	0.40[b]
Bronchodilator drugs[c]	8.66 (3.92)	8.89 (3.29)	0.16[b]

[a] Chi-square, [b] T-tes, [c] Mean (SD) was reported.

Table 2. Comparison of arterial blood gases parameters between intervention and control groups

Variable	Intervention group	Control group	*P* value[a]	Effect size
	Mean (SD)	Mean (SD)		
pH				
Day1	7.352 (0.09)	7.34 (0.07)		
Day2	7.38 (0.06)	7.34 (0.09)	0.26	0.01
Day3	7.38 (0.05)	7.35 (0.15)		
PaCO2				
Day1	36. 17 (11.39)	37.08 (9.62)		
Day2	34.12 (8.97)	35.36 (8.54)	0.21	0.02
Day3	36.43 (7.92)	35.3 (9.03)		
HCO3				
Day1	19.55 (4.29)	19.55 (4.16)		
Day2	19.80 (4.88)	19.86 (5.02)	0.20	0.02
Day3	21. 35 (4.33)	19.96 (5.39)		
SaO2				
Day1	95.66 (2.91)	96.11 (1.99)		
Day2	96.86 (3.07)	96.43 (2.04)	0.001*	0.12
Day3	97.2 (2.33)	95.14 (3.06)		
PaO2				
Day1	101.38 (50.76)	70.89 (36.2)		
Day2	103.70 (48.59)	78.76 (33.05)	<0.001*	0.18
Day3	100.4 (38.63)	82.72 (33.75)		
BE				
Day1	4.4 (4.2)	4.6 (4.3)		
Day2	3.8 (2.7)	3.9 (2.4)	0.33	0.02
Day3	3.7 (3.7)	3.8 (2.7)		

[a] Repeated measure analysis of variance (ANOVA), *Statistically significant.

Eucalyptus, as a bronchodilator, has not been recognized properly, the results of present study and changes in PaO2 and SaO2 indicated the positive effects of Eucalyptus on improving oxygenation in patients undergoing MV.

As far as the researchers investigated, limited studies have investigated the effects of Eucalyptus, as an aerosol, in patients undergoing MV in ICUs.[24,25] A study showed that NE can reduce the incidence of ventilator-associated pneumonia (VAP).[24] Also, Amini et al found that NE can reduce microbial contamination of ETT biofilm in ventilated patients.[25] Keane et al showed that VAP is most likely to increase the PaO2/FiO2 ratio; therefore, reduced

Table 3. Comparison of vital signs, GCS, TV, and PIP between intervention and control groups

Variable	Intervention group	Control group	*P* value[a]	Effect size
	Mean (SD)	Mean (SD)		
RR				
Day1	17.06 (5.73)	17.51 (6.3)		
Day2	17.60 (6.49)	17.60 (6.3)	0.88	0.002
Day3	17.34 (5.76)	17.83 (6.75)		
T				
Day1	37.18 (0.54)	37.2 (0.59)		
Day2	37.28 (0.67)	37.2 (0.7)	0.42	0.01
Day3	37.31 (0.74)	37.21 (0.88)		
HR				
Day1	90.97 (20.79)	90.94 (19.90)		
Day2	91.57 (20.17)	88.57 (23.16)	0.82	0.002
Day3	92.11 (14.71)	87.31 (23.17)		
DBP				
Day1	81.94 (18.45)	77.69 (14.17)		
Day2	79.54 (12.51)	78.46 (17.60)	0.42	0.01
Day3	78.31 (15.71)	76.94 (13.78)		
SBP				
Day1	129.31 (23.44)	125.86 (19.30)		
Day2	124.46 (17.07)	123.17 (22.44)	0.32	0.01
Day3	127.69 (21.56)	123.06 (27.16)		
GCS				
Day1	6.23 (2.41)	6.91 (2.8)		
Day2	7.26 (2.65)	7.31 (2.76)	0.56	0.08
Day3	8.03 (3.63)	7.71 (3.46)		
TV				
Day1	506.83 (102.113)	496.86 (104.08)		
Day2	502.03 (154.98)	511.57 (156.19)	0.96	0.001
Day3	503.29 (143.42)	507.69 (144.68)		
PIP				
Day1	19.63 (5.04)	16.60 (3.59)		
Day2	17.34 (3.76)	17.11 (3.34)	0.001*	0.12
Day3	16.66 (4.55)	18.89 (4.15)		

RR: Respiratory rate, BT: Body temperature, HR: Heart rate, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, GCS: Glasgow coma scale, TV: Tidal volume, PIP: Peak inspiratory pressure.
[a] Repeated measure Analysis of variance (ANOVA); *Statistically significant.

incidence of pneumonia and microbial load of ETT may be one of the reasons for oxygenation improvement in ventilated patients.[31] Moreover, another study found that VAP can deteriorate oxygenation conditions.[32] PaO2 improvement in patients who received inhaled Eucalyptus was significantly associated with reducing PIP due to the bronchodilator properties of Eucalyptus and reducing airway resistance. Cineole, as the main ingredient of Eucalyptus, is exclusively used in inflammatory airway diseases, and as a mucolytic agent, it has positive effects on mucociliary function and mucociliary clearance; it also has bronchodilator and anti-inflammatory properties. Studies showed that intake of cineole 200 mg three times a day for 6 months can reduce the symptoms of dyspnea and improve pulmonary function and health status of patients with COPD.[33-35]

Use of inhaled medications in mechanically ventilated patients can reduce airway resistance, facilitate dilution and pulmonary secretion drainage, and prevent or treat airway infection.[26,27] Patients under MV with respiratory failure often require auxiliary treatments to relieve their symptoms. Inhaled medications reduce airway obstruction and improve gas exchange.[4,10] Cineole in Eucalyptus has anti-inflammatory and mucolytic properties.[23] It acts as a potent inhibitor of tumor necrosis factors and interleukin. It also acts as a potent factor for controlling the increased mucus secretion by inhibiting cytokine, indicating that it can reduce the severity of asthma, COPD, and sinusitis.[36]

Other methods of complementary medicine such as therapeutic touch,[4] massage therapy and reflexology,[37-39] and sensory stimulation provided by family[40] can improve arterial blood saturation and PaO2 in mechanically ventilated patients, which is attributed to restlessness and anxiety reduction. According to the results of the current study, there was no significant difference between the study groups in terms of vital signs (temperature, respiratory rate, pulse rate, diastolic blood pressure, and systolic blood pressure) as well as TV and GCS. To the best of our knowledge, no study has mentioned the effect of Eucalyptus on these indicators. However, since mechanically ventilated patients have hemodynamic disorders, which usually requires medicinal interventions, unchanged status of these indicators can be advantageous.

One of the limitations of current study is its relatively small sample size conducted in a single center, which reduces its generalizability. It is recommended to investigate the effect of Eucalyptus in certain groups of critically ill patients. The short duration of study was another limitation of the study. Increasing the duration of study and investigating other measures such as duration of hospitalization and mortality could help to better understood the effects of Eucalyptus on patients.

Conclusion

Nebulized Eucalyptus can improve oxygenation and reduce airway pressure in patients undergoing MV. However, there was no significant difference between the intervention and control groups in terms of vital signs (body temperature, respiratory rate, pulse rate, diastolic blood pressure, and systolic blood pressure) as well as TV and GCS.

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Authors' Contributions

NA: Contributed to the conception, design, and data collection

Research Highlights

What is the current knowledge?

Oxygenation disorders and increased airway resistance in mechanically ventilated patients have created incentives for using new therapies such as inhaled medicine.

What is new here?

Nebulized Eucalyptus can improve oxygenation and reduce airway pressure in patients undergoing mechanical ventilation.

process. MH: Helped in data collection process. KR and AY: Supervised the study, contributed to the design of the study, and reporting of the result. MS: Contributed to analysis, interpretation, and reporting. All authors contributed to drafting, revising, and preparing the final version of the manuscript. All authors met the authorship criteria.

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Data Accessibility

The datasets are available from the corresponding author on reasonable request.

Ethical Issues

The current study is part of an MSc thesis approved by the Ethics Committee of Arak University of Medical Sciences, Iran (code: IR.ARAKMU.REC.1393-165-3) and registered in the Iran Registry of Clinical Trials (no: IRCT2014060217955N1). An informed consent was obtained from the patients' legal guardian, and they were free to withdraw from the study without any changes in their treatment.

Conflict of Interests

The authors declared no conflict of interests.

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