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, and PaO2, and the peak inspiratory pressure (PIP) and tidal volume (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; it improves gas exchange both in alveoli and tissue surfaces by facilitating inhalation and exhalation. 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. 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. Although MV is a vital part of saving critical ill patients, the use of this method is also associated with complications. 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. 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. 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. ABG provides useful information about ventilation, oxygenation, and acid-base balance status in patients. 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.

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

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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. Furthermore, use of alveolar recruitment maneuver improves oxygenation in patients with acute respiratory failure undergoing pressure support ventilation. 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. 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. 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. 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. 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. 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. 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.

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. 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. 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.

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. 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. 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.

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, 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. 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 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
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 1. Patient characteristics in two intervention and control groups

| Variable                        | Intervention group | Control group | P value α |
|---------------------------------|--------------------|--------------|-----------|
| Gender                          | N (%)              | N (%)        | 0.78      |
| Male                            | 27 (77.1)          | 26 (74.3)    |           |
| Female                          | 8 (22.9)           | 9 (25.7)     |           |
| Cause of hospitalization        |                    |              | 0.31      |
| Multiple trauma                 | 16 (54.7)          | 13 (37.1)    |           |
| Post-operative                  | 9 (25.7)           | 15 (42.9)    |           |
| Medical                         | 10 (28.6)          | 7 (20)       |           |
| Invasive interventions          |                    |              | 0.19      |
| CV line                         | 9 (25.7)           | 13 (37.1)    |           |
| 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)    | 0.47      |
| Death                           | 13 (37.1)          | 12 (34.3)    |           |
| 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                             | 48.9 (17.17)       | 54.2 (13.99) | 0.16β    |
| Duration of intubation          | 6.11 (3.16)        | 6.66 (3.62)  | 0.50β     |
| Antibiotics drugs†              | 1.83 (1.07)        | 2.03 (0.92)  | 0.40β     |
| Bronchodilator drugs‡           | 8.66 (3.92)        | 8.89 (3.29)  | 0.16β     |

α Chi-square, β T-tes, † Mean (SD) was reported.

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

| Variable | Intervention group | Control group | P value α | Effect size |
|----------|--------------------|---------------|-----------|-------------|
| pH†      |                    |               |           |             |
| Day1     | 7.352 (0.09)       | 7.34 (0.07)   | 0.26      | 0.01        |
| Day2     | 7.38 (0.06)        | 7.34 (0.09)   |           |             |
| 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)  |           |             |
| PaO2     |                    |               |           |             |
| Day1     | 95.66 (2.91)       | 96.11 (1.99)  |           |             |
| Day2     | 96.86 (3.07)       | 96.41 (2.04)  | 0.001†    | 0.12        |
| Day3     | 97.2 (2.33)        | 95.14 (3.06)  |           |             |
| SaO2     |                    |               |           |             |
| Day1     | 95.66 (2.91)       | 96.11 (1.99)  |           |             |
| Day2     | 96.86 (3.07)       | 96.41 (2.04)  |           |             |
| 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 (31.75) |           |             |
| 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)     |           |             |

†Repeated measure analysis of variance (ANOVA), †Statistically significant.
Nebulized eucalyptus and arterial blood gases

Moreover, another study found that 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.30-35

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.40 Cineole in Eucalyptus has anti-inflammatory and mucolytic properties.22 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, massage therapy and reflexology,17-19 and sensory stimulation provided by family and friends 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.

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.

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

| Variable | Intervention group | Control group | P value* | Effect size |
|----------|-------------------|---------------|----------|-------------|
| RR       |                   |               |          |             |
| Day1     | 17.06 (5.73)      | 17.51 (6.3)   | 0.88     | 0.002       |
| Day2     | 17.60 (6.49)      | 17.60 (6.3)   |          |             |
| Day3     | 17.34 (5.76)      | 17.83 (6.75)  |          |             |
| T        |                   |               |          |             |
| Day1     | 37.18 (0.54)      | 37.2 (0.59)   | 0.42     | 0.01        |
| Day2     | 37.28 (0.67)      | 37.2 (0.7)    |          |             |
| 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 (21.16) | 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 (144.66)|         |             |
| 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 (4.5)   |          |             |

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.

*Repeated measure Analysis of variance (ANOVA); 'Statistically significant.
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. 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.

References
1. Pan C, Qiu H. Improve survival from prolonged mechanical ventilation: beginning with first step. J Thorac Dis. 2015; 7 (7): 1076-9. doi: 10.3978/j.issn.2223-4482.2015.07.13
2. Fontela PC, Prestes RB, Forgiarini LA Jr, Friedman G. Variable mechanical ventilation. Rev Bras Ter Intensiva. 2017; 29 (1): 77-86. doi: 10.5935/0103-507x.20170012
3. Zamzam MA, Abd El Aziz AA, Elhefnawy MY, Shaheen NA. Study of the characteristics and outcomes of patients on mechanical ventilation in the intensive care unit of El-Mahalla Chest Hospital. Egypt J Chest Dis Tuberc. 2015; 64 (3): 693-701. doi: 10.1016/j.ejcdt.2015.04.001
4. Baghcabethi N, Koohestani H, Dabirian A, Alavi Majd H. Determining the effect of touch on arterial blood oxygen saturation in neonates with respiratory distress syndrome. J Arak Uni Med Sci. 2007; 10 (1): 10-7. [Persian]
5. Rittayamai N, Brochard L. Recent advances in mechanical ventilation in patients with acute respiratory distress syndrome. Eur Respir Rev. 2015; 24 (135): 132-40. doi: 10.1183/09059180.00021414
6. Barton G, Vanderspake-Wright B, Shea J. Optimizing oxygenation in the mechanically ventilated patient: nursing practice implications. Crit Care Nurs Clin North Am. 2016; 28 (4): 425-35. doi: 10.1016/j.cnc.2016.07.022
7. Snoek KG, Capolupo I, van Rosmalen J, Hout Lde J, Vlijthuize S, Greenough A, et al. Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia: a randomized clinical trial (the VICI-trial). Ann Surg. 2016; 263 (5): 867-74. doi: 10.1097/sla.0000000000001533
8. Martin CM, Priestap F. Agreement between venous and arterial blood gas analysis of acid-base status in critical care and ward patients: a retrospective cohort study. Can J Anaesth. 2017; 64 (11): 1138-43. doi: 10.1016/s1263-0171-0931-8
9. Dennis D, Torre L, Baker S, Helden-Todd T. A snapshot of the oxygenation of mechanically ventilated patients in one Australian intensive care unit. Anaesth Intensive Care. 2017; 45 (3): 359-64. doi: 10.1177/0310057x1704500311
10. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013; 41 (2): 423-32. doi: 10.1097/ccm.0b013e31826a44f6
11. Koulouras V, Papathanakos G, Papathanasiou A, Nakos G. Efficacy of prone position in acute respiratory distress syndrome patients: a pathophysiology-based review. World J Crit Care Med. 2016; 5 (2): 121-36. doi: 10.5492/wjccm.v5.i2.121
12. Dalmedico MM, Salas D, Oliveira AM, Baran FDP, Meardi JT, Santos MC. Efficacy of prone position in acute respiratory distress syndrome: overview of systematic reviews. Rev Esc Enferm USP. 2017; 51: 63251. doi: 10.1590/s1980-220x201648803251
13. Lovas A, Németh MF, Trásy D, Molnár Z. Lung recruitment can improve oxygenation in patients ventilated in continuous positive airway pressure/support pressure mode. Front Med (Lausanne). 2015; 2: 25. doi: 10.3389/fmed.2015.00025
14. Lovas A, Molnár Z. Alveolar recruitment in patients with assisted ventilation: open up the lung in spontaneous breathing. In: Vincent JL, ed. Annual Update in Intensive Care and Emergency Medicine 2018. Cham: Springer; 2018. p. 205-15. doi: 10.1007/978-3-319-73670-9_17
15. Young CC, Harris EM, Vaccchino C, Bodnar S, Bukowy B, Elliott RRD, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth. 2019; 123 (6): 898-913. doi: 10.1016/j.bja.2019.08.017
16. Standeford TJ, Ward PA. Therapeutic targeting of acute lung injury and acute respiratory distress syndrome. Transl Res. 2016; 167 (1): 183-91. doi: 10.1016/j.trsl.2015.04.015
17. Lai MY, Chu SM, Lakshminrusimha S, Lin HC. Beyond the inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Pediatr Neonatol. 2018; 59 (1): 15-23. doi: 10.1016/j.pedneo.2016.09.011
18. Yu B, Ichinose F, Bloch DB, Zapol WM. Inhaled nitric oxide. Br J Pharmacol. 2019; 176 (2): 246-55. doi: 10.1111/bph.14512
19. Ariel A, Altraja A, Belevskiy A, Boros PW, Danila E, Fečar M, et al. Inhaled therapies in patients with moderate COPD in clinical practice: current thinking. Int J Chron Obstruct Pulmon Dis. 2018; 13: 45-56. doi: 10.2147/copd.v145573
20. de Lima Gondim F, dos Santos GR, do Nascimento IF, Serra DS, Cavalcante FS. Beneficial effects of eucalyptol in patients with moderate COPD: a proposal for alternative pharmacological therapy for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth. 2019; 123 (6): 898-913. doi: 10.1016/j.bja.2019.08.017
21. Sudhoff H, Kleenke C, Greiner JJ, Müller J, Brotzmann V, Ebmeyer J, et al. 1,8-cineole reduces mucus-production in a novel human ex vivo model of late rhinosinusitis. PLoS One. 2015; 10 (7): e0133040. doi: 10.1371/journal.pone.0133040
22. Worth H, Dethlen U. Patients with asthma benefit from concomitant therapy with cineole: a placebo-controlled, double-blind trial. J Asthma. 2012; 49 (8): 849-53. doi: 10.3109/02770903.2012.717657
Nebulized eucalyptus and arterial blood gases

23. Fischer J, Dethlefsen U. Efficacy of cineole in patients suffering from acute bronchitis: a placebo-controlled double-blind trial. Cough. 2013; 9 (1): 25. doi: 10.1186/1745-9974-9-25

24. Amini N, Rezaei K, Yazdannik A. Effect of nebulized eucalyptus on contamination of microbial plaque of endotracheal tube in ventilated patients. Iran J Nurs Midwifery Res. 2016; 21 (2): 165-70. doi: 10.4103/1735-9066.178242

25. Amini N, Rezaei K, Bahrami M, Yazdannik A. Effect of nebulized eucalyptus on ventilator associated pneumonia in ventilated patients. J Med Plants. 2019; 18 (72): 299-307. doi: 10.29252/jmp.4.72.299

26. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. Ann Am Thorac Soc. 2014; 11 (3): 425-34. doi: 10.1513/AnnalsATS.201311-395FR

27. Angoulvant F, Bellêttre X, Milcent K, Teglas JP, Claudet I, Le Guen CG, et al. Effect of nebulized hypertonic saline treatment in emergency departments on the hospitalization rate for acute bronchiolitis: a randomized clinical trial. JAMA Pediatr. 2017; 171 (8): e171333. doi: 10.1001/jamapediatrics.2017.1333

28. Bohrgardt JM, Kloft C, Sharma A. Inhaled therapy in respiratory disease: the complex interplay of pulmonary kinetic processes. Can Respir J. 2018; 2018: 2732017. doi: 10.1155/2018/2732017

29. Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H. Medicinal plants: past history and future perspective. J Herbmed Pharmacol. 2018; 7 (1): 1-7. doi: 10.15171/jhp.2018.01

30. Bachir RG, Benali M. Antibacterial activity of the essential oils from the leaves of Eucalyptus globulus against Escherichia coli and Staphylococcus aureus. Asian Pac J Trop Biomed. 2012; 2 (9): 739-42. doi: 10.1016/s2221-1691(12)60220-2

31. Keane S, Vallecoccia MS, Nseir S, Martin-Loeches I. How can we distinguish ventilator-associated tracheobronchitis from pneumonia? Clin Chest Med. 2018; 39 (4): 785-96. doi: 10.1016/j.ccm.2018.08.003

32. Damas P, Frrippiat F, Ancion A, Canivet JL, Lambermont B, Layios N, et al. Prevention of ventilator-associated pneumonia and ventilator-associated conditions: a randomized controlled trial with subglottic secretion suctioning. Crit Care Med. 2015; 43 (1): 22-30. doi: 10.1097/ccc.0000000000000674

33. Juergens UR. Anti-inflammatory properties of the monoterpene 1.8-cineole: current evidence for co-medication in inflammatory airway diseases. Drug Res (Stuttg). 2014; 64 (12): 638-46. doi: 10.1055/s-0034-1372609

34. Alschuler L, Chiasson AM, Horwitz R, Sternberg E, Crocker R, Weil A, et al. Integrative medicine considerations for convalescence from mild-to-moderate COVID-19 disease. Explore (NY). 2022; 18 (2): 140-8. doi: 10.1016/j.explore.2020.12.005

35. Kardos P, Khaletskaya O, Kropova O. Efficacy and safety of cineole (Soledum®) in the treatment of patients with acute bronchitis: results of an open-label randomized clinical phase III study. Clin Phytosci. 2021; 7 (1): 83. doi: 10.1186/s40816-021-00319-8

36. Brown SK, Garver WS, Orlando RA. 1,8-cineole: an underappreciated anti-inflammatory therapeutic. J Biomed Res Ther. 2017; 6 (1): 154. doi: 10.4172/2167-7956.1000154

37. Ramezani T, Baniasadi H, Baneshi MR. The effects of massage on oxygen saturation of infants with respiratory distress syndrome treated with nasal continuous positive airway pressure. Br J Pharm Res. 2017; 16 (5): 1-7. doi: 10.9734/bjpr/2017/32751

38. Kaur J, Kaur S, Bhardwaj N. Effect of ‘foot massage and reflexology’ on physiological parameters of critically ill patients. Nurs Midwifery Res J. 2012; 8 (3): 223-33. doi: 10.1177/0974150x20120305

39. Hatefi M, Jaafarpour M, Khani A, Khajavikhan J, Kokhazade T. The effect of whole body massage on the process and physiological outcome of trauma ICU patients: a double-blind randomized clinical trial. J Clin Diagn Res. 2015; 9 (6): UC05-8. doi: 10.7860/jcdr/2015/12756.6096

40. Yousefi H, Naderi M, Daryabeigi R. The effect of sensory stimulation provided by family on arterial blood oxygen saturation in critical care patients. Iran J Nurs Midwifery Res. 2015; 20 (1): 63-8.