Effect of Nebulized Eucalyptus for Preventing Ventilator-Associated Pneumonia in Patients under Mechanical Ventilation: A Randomized Double Blind Clinical Trial

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SUBJECT AREAS
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Abstract
Background: Pneumonia caused by the ventilator is the most common acquired infection in the intensive care unit, which increases the morbidity and mortality of the patients. Eucalyptus plant has antiseptic properties. Therefore, the present study investigates the effect of eucalyptus incense on prevention of pneumonia in patients with endotracheal tube in the intensive care unit. Methods: This clinical trial study was performed on 100 patients under ventilation in two intervention and control groups in Imam Reza Hospital, Kermanshah, Iran in 2018. The patients in the intervention group, Eucalyptus solution 2% and in the control group received 10 cc distilled water as an inhaler three times a day. The results of the two groups were compared to the incidence of pulmonary infections based on CPIS criteria and compared with SPSS version 19 software. Results: The incidence of late pneumonia was significantly lower in the intervention group (P=0.02). The onset of pneumonia significantly later in the intervention group than the control group (P=0.01). The prevalence of Klebsiella, Candida albicans, and Staphylococcus aureus was significantly decreased in the intervention group (P=0.02) (P=0.04) (P=0.01). Conclusion: The results of this study showed that eucalyptus inhalation is effective in reducing the incidence of pulmonary infection in patients under ventilation. It is recommended that these products be used to prevent pulmonary infections in these patients.

Background
Ventilator-Associated Pneumonia (VAP) is the most common infection among patients with the endotracheal tube and mechanical ventilation in the Intensive Care Unit (ICU) [1]. Its prevalence is 10%-65% and it is 5-10 times more common in ICUs than in other wards [2]. The risk of pneumonia increases in intubated patients due to the easier accessibility of the lower respiratory tract by the colonizing bacteria at the end of the pharynx [3, 4].
VAP is defined as noso-comial pneumonia in mechanically ventilated patients that develops more than 48 hours after initiation of mechanical ventilation [5]. It associated with increased mortality 30%-70%, disability, longer ICU stays, longer hospitalization, longer duration of mechanical ventilation, and higher costs of treatment [6-8].
Occurrence of VAP increases health system costs; thus, any intervention to reduce VAP will result in reducing costs, morbidity and mortality [9].

Numerous studies have assessed various strategies for VAP prevention, which can be classified into pharmacologic and non-pharmacologic interventions. The VAP treatment is mainly via antibiotics, but evidence suggests that the unnecessary use of antibiotics has given rise to antibiotic resistance and the development of resistant bacteria. Over the past few years, the interest in natural medicine has been increasing in industrialized societies particularly against microbial agents because of the ever growing problem of antibiotic resistance [10]. It Condition led to renewed interest in plants to investigate their antibacterial activities [11].

Eucalyptus is one of the most famous herbs that grow from a species belonging to the Mytracease family that grows in tropical and subtropical regions, and includes about 800 to 900 species, which have long been considered as antimicrobial and other properties [12]. The Eucalyptus globulus is best known for all of them [13]. Eucalyptus is used to treat many diseases, such as influenza, sinusitis, pneumonia, asthma, throat ulcer, bronchitis, tonsillitis (tonsillectomy), bloody diarrhea and skin diseases. Leaf extract of this plant has anti-inflammatory, analgesic, antifungal, anti-viral and antioxidant effects.

The extract of this plant is also used for a wide range of Gram-negative and Gram-positive bacteria such as: Klebsiella, Staphylococcus aureus, Hemophilus influenza, Streptococcus pneumoniae, Streptococcus papenus, Streptococcus saglactiae, Pseudomonas aererosos, Shigella vulgaris, Salmonella typhi, Escherichia coli and Candida albicans [14-17].

Previous studies have found that Eucalyptus globulus is also effective on respiratory pathogens [18]. The use of a nebulizer is one of the recommended methods for the delivery of antibiotics and other antimicrobial extracts to the inferior airways of ventilated patients [19].

The increased prevalence and complexity of multidrug-resistant organisms in hospital-acquired infections has created incentives for the use of new therapies such as inhaled agents, which are considered for the prevention and treatment of pneumonia

According to the antimicrobial properties of plant and also complications that VAP can have for
patients, the aim of this study was to evaluate the effect of Eucalyptus incense on the prevention of VAP in patients with endotracheal tube in the ICU of Imam Reza Hospital, Kermanshah, Iran.

Methods

This randomized, paralleled group, double-blind, placebo-controlled clinical trial was conducted in patients with the tracheal tube under mechanical ventilation in the ICU of Imam Reza Hospital, Kermanshah, Iran, in 2018. This study is registered on IRCT.Ir (Ref. No: IRCT2017010727819N2) in the Iranian.

The research population was the study of patients under mechanical ventilation in Imam Reza Hospital. The sample of the study was patients undergoing mechanical ventilation, which had criteria for entry into the study.

Inclusion criteria

Inclusion criteria for the study included: not having lung infections and lung disease on admission, No history and avoiding the use of immunosuppressive drugs, aged 40 to 70 years, not having sensitivity to Eucalyptus examining case histories and their relatives, patients intubated less than 6 hours, Not taking of antibiotics, No history of diabetes, level of consciousness (GCS) 3 to 8

Exclusion criteria: patient transport to ward, hemodynamic disorders, liver complications, the occurrence of urticaria, petechiae, itch and allergy symptoms eucalyptus, extubation and mortality, the occurrence of any bad conditions or serious problems in the patient during the examination.

Recruitment/randomization

To determine the sample size of the study, the proportion of VAP after >5 days, was obtained from the study by Lorente et al [20], Considering 95% confidence interval and a power 80%, the sample size was calculated to be 50 patient in each group.

In this study, 100 intubated patients who hospitalized in the intensive care unit divided into two intervention and control group. The patients were randomly divided according to even and odd numbers of patient’s record in two groups.

Intervention

Patients under mechanical ventilation were treated according to the SIMV model and the ventilation
device was adjusted with PEEP = 5CmH2o and Sigh = 5 / min.

In the intervention group, 4 cc Eucalyptus 5% (The Eucalyptus Globulus Product of Yellow Band Co., Shahrekord, Iran) Diluted with 6 cc normal saline [21], and In the control group, 10 cc of distilled water was given by a nebulizer kit through a mechanical ventilation inspiratory system every 8 hours daily about 20 minutes.

Eucalyptus or placebo prescriptive (similar to the appearance of Eucalyptus incense solution) was performed by a collaborator in each of the groups. The other partner's information partner, as well as the patients themselves, did not know how to go into each group (intervention and control). Patients were examined by an Infectious specialist with a Clinical Pulmonary Infection Score (CPIS) for early (Up to 96 hours from the time of airway intubation) and delay VAP (after 96 hours) [22] daily.

Outcome measure (CPIS Scale)

This score was developed by Pugin et al. in 1991 and confirmed by the National Center for Infectious Diseases [7]. The CPIS scale includes body temperature, white cell count, tracheal aspirates in terms of color and smell, oxygenation (PaO2/FiO2), radiographic findings (chest X-ray), and positive tracheal aspirate culture. In this scale, for each criterion, the score is from 2 to 0 and the maximum score is 10. A score of six or higher shows the presence of pneumonia (CPIS ≥ 6).

The information contained age, sex, the cause of admission, diagnosis VAP in both groups were recorded. Standard routine care (airway suction, physiotherapy, patient position, tuberculosis cuff pressure test in each shift, oral hygiene and prophylaxis of gastrointestinal ulcers (pentazole) in patients with endotracheal tract in both groups were identical, as well as, antibacterial filters are connected to the ventilators in both groups according to routine care.

Statistical Analysis

The data collected in the present study were analyzed by SPSS software, version 19. The qualitative results were reported as absolute frequency and relative frequency, while the quantitative results were expressed as the mean ± standard deviation (SD). The data analysis was performed using the independent t-test, and chi-square. The level of significance was set at P < 0.05.

Results
In this study, 100 patients with the endotracheal tube under mechanical ventilation were evaluated in both intervention and control groups. There was no significant difference between the study groups regarding age, sex, disease and hospitalization reasons, and the two groups were homogeneous in terms of the underlying variables (Table 1).

The incidence of both early and delay pneumonia was lower in the intervention group than in the control group, but this decrease was significant only in delay pneumonia (Table 2).

The onset of pneumonia related to mechanical ventilation in the intervention and control groups was 7.66±3.49 and 5.48±2.04 day, respectively; it was significantly in the intervention group (P=0.01).

The overall incidence of VAP (early and delay) in the intervention and control group was 15 (30%) and 29 (58%), respectively, which was statistically significant (P=0.005).

11 cases VAP (22%) was found in patients with Brain Ischemia that was the highest incidence. The frequency of bacterial VAP agents was shown in the table (Table 3).

The most common bacterial agents of VAP in the control group were Acinetobacter (16%), Staphylococcus aureus (16%) and Citrobacter (12%), respectively (Table 3).

The most common bacterial agents of VAP in the intervention group were Acinetobacter (12%) and Citrobacter (8%), respectively (Table 3).

Based on the results of trachea secretion culture tests, in the intervention and control group, 6 and 8 different bacterial agents were observed, respectively, that was not statistically significant (P=0.56).

In 13 cases (26%) VAP of control group, the cause of the infection was two bacteria, while, only 6 cases (12%) observed in the intervention group, that was not statistically significant (P=0.07).

The frequency of pneumonia was lower in the intervention group than in the control group, however, there was a significant decrease in the factors of Klebsiella, Candida and Staphylococcus aureus (Table 3).

Discussion

In the present study, the incidence and onset of VAP in the group receiving eucalyptus incense differed significantly from the control group. In a study conducted without a control group, it was concluded that eucalyptus incense can reduce colonization of common nosocomial pathogens and the
incidence of pneumonia related to mechanical ventilation [23] that is consistent with our results. The airways may be colonized by different microorganisms. The most common microorganisms colonizing the airways were K. pneumonia and A. baumannii [24-26]. However, in a number of other studies, Acinetobacter and Pseudomonas were more common [27-28]. The study by Amini et al. was conducted to investigate the effects of Eucalyptus incense on colonies in the tracheal tube. The results of this study showed that the colony of infectious agents in the intervention group was significantly lower; also, Klebsiella and Staphylococcus aureus showed higher sensitivity to Eucalyptus [29]. It is consistent with our study in relation to reduce microbial contamination and type of bacteria of VAP. Also, in an experimental study, the positive effects of Eucalyptus antimicrobial on Klebsiella, Pseudomonas, Escherichia coli, and Staphylococcus aureus species were observed [30]. The result of another study showed to reduce the microbial load of ETT, eucalyptus significantly reduced K. pneumonia contamination in the intervention group [21]. The study by Fabio et al., the antimicrobial properties of eucalyptus was evaluated on Klebsiella, E. coli, Proteus, Pseudomonas, and St. aureus. They found that K. pneumonia and E. coli had the highest sensitivity and Pseudomonas and Proteus had the least sensitivity to eucalyptus [31].

In a study by Elaissi et al. the best antimicrobial activity of Eucalyptus was observed against Staphylococcus aureus, Haemophilus influenza, Streptopapogen, Streptococcus pneumonia [16]; that is consistent with our study results for Staphylococcus and Streptococcus. Boukhatem and his colleagues have suggested that Eucalyptus globulus has a more antibacterial effect on gram-positive bacteria than gram-negative bacteria. They also reported strong antibacterial effects of eucalyptus in the incense phase [24] that is consistent with our research findings about Staphylococcus aureus. The study by Soyinge and colleagues reported the effectiveness of eucalyptus against infectious respiratory microorganisms [19]. The study of Tiewsoh et al., Streptococcus pneumonia, Staphylococcus aureus, and acinetobacter reported as the most common infection pulmonary. Also, Enterobacter, Klebsiella, Pseudomonas as the least common cause of pneumonia [32].

According to the Neelam’s study, the number of two-microbial infections in the two groups was equal, but in our study, the frequency of the number of agents in the Eucalyptus group was lower. The
antimicrobial effects of eucalyptus are attributed to the 1 and 8 cineol [33]. Considering the effects of eucalyptus on antibacterial effects, use the inhaler form of this plant can deliver a large concentration of it to the lungs under mechanical ventilation.

One of the causes of differences in pulmonary infections in various studies can be the excessive use of antibiotics and antibiotic resistance. Also, other interventions (suction, mouthwash, position, use of corticosteroids) in the intensive care unit can be of great importance in the incidence and type of VAP agent. Today, due to bacterial resistance, they do not respond to common antibiotics in treatment and cause complications such as lung abscesses, meningitis, pleural effusion, increased length of hospitalization and more pneumonia, increased therapeutic costs, and increased mortality and morbidity [34]. Using the inhaler and respiratory form of drugs is an effective way to deliver the drug to the target organ and reduce the dose and side effects [35].

From the strengths of the study, this study was conducted for the first time in patients with endotracheal tube and for the prevention of pulmonary infections. Also, the use of the inhaler form of this product was first used in patients with endotracheal tube. This product was not evaluated under laboratory conditions with infectious agents derived from pulmonary patients with endotracheal tube for efficacy on bacterial colonies, this was one of the weaknesses in the study.

One limitation of the study was the lack of collaboration of the team with the researchers in some cases. Restrictions were fixed by giving full explanations and expressing the objectives of the study. Creating and analyzing the Eucalyptus inhaler form was another limitation. This work was carried out by pharmacologists in the lab and the product was created as an inhaler.

Considering the antibacterial effects of this product, it is recommended to investigate its effects on various types of patients and to prevent and treat various infectious diseases. Also, by extraction of the active ingredient and its conversion to various forms of injectable and oral administration, various methods of drug delivery to the body and its effects are evaluated. The pharmacodynamic and pharmacokinetic study of this product can provide further results for its efficacy and mechanism.

Conclusion
Patients undergoing mechanical ventilation are exposed to increased morbidity and mortality due to
increased risk of pulmonary infection. According to the results, Eucalyptus is effective as a prophylaxis or delay in the development of pulmonary infection in patients under ventilation. It is recommended to use this plant in patients with the tracheal tube.

Declarations
Ethics approval and consent to participate
This study was approved by the ethics committee of Kermanshah University of medical sciences, Kermanshah, Iran (With approval NO. IR.kums.REC.1395.592). Informed written consents were obtained from patients or their legal guardians and they were assured of the anonymity and confidentiality of private information.
Consent for publication
Not applicable.
Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Competing interests
The authors declare that they have no competing interests
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Authors' contributions
Aminisaman J helped in designing, conducting the study, and revise the manuscript. Hemmatpour B, Mohammadi S and Mirzaei M helped in designing the study and collecting the data. Karimpour H helped in designing the study, interpret the data data and writing the manuscript. Kawyannejad R helped in designing and conducting the study and writing the manuscript. All authors read and approved the final manuscript.
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**Table 1. Patient Characteristics In Two Intervention And Control Groups**

| Variables                      | Intervention group (N = 50) | Control group (N = 50) |
|--------------------------------|----------------------------|------------------------|
|                                | Age (year)                 |                        |
|                                | 43.74(12.98)**             | 46.84(13.6)**          |
|                                | Sex*                       |                        |
|                                | Woman                      | 28(56)                 | 31(62)                 |
|                                | Man                        | 22 (44)                | 19(38)                 |
|                                | Cause of hospitalization*  |                        |
|                                | Brain hemorrhage           | 6(12)                  | 13(26)                 |
|                                | Brain ischemia             | 18(36)                 | 13(26)                 |
|                                | Trauma                     | 9(18)                  | 4(8)                   |
|                                | Asthma                     | 6(12)                  | 3(6)                   |
|                                | Brain Tumor                | 2(4)                   | 6(12)                  |
|                                | Acute Renal failure        | 4(8)                   | 4(8)                   |
|                                | Post CPR                   | 5(10)                  | 7(14)                  |

* It is reported as frequencies and percentages\ # based on independent t test\& based on chi-square test
** It is reported as mean and standard deviation

**Table 2. Frequency Of Early And Delay Pneumonia In The Intervention And Control Groups**

| A type of pneumonia | Intervention group Number (%) | Control group Number (%) | P value* |
|---------------------|-------------------------------|--------------------------|----------|
| Early               | 6(12%)                        | 10(20%)                  | 0.27     |
| Delay               | 9(18%)                        | 19(38%)                  | 0.02     |
* Chi square test

Table 3. Frequency Of Type Of Agent Of Pulmonary Infection In Patients Under Mechanical Ventilation In Intervention And Control Groups

| Type of microorganism agent | Intervention group Number (%) | Control group Number (%) | P value* |
|-----------------------------|--------------------------------|--------------------------|----------|
| Escherichia coli            | 3(6%)                          | 5(10%)                   | 0.46     |
| Klebsiella                  | 1(2%)                          | 7(14%)                   | 0.02     |
| Pseudomonas                 | 4(8%)                          | 5(10%)                   | 0.72     |
| Pseudomonas                 | 6(12%)                         | 8(16%)                   | 0.37     |
| Acinetobacter               | 0(0)                           | 3(6%)                    | 0.01     |
| Candida                     | 5(10%)                         | 6(12%)                   | 0.74     |
| Citrobacter                 | 2(4%)                          | 8(16%)                   | 0.04     |
| Staphylococcus aureus       | 0(0)                           | 2(4%)                    | 0.15     |

* Chi square test

Figures
A convenience sample of eligibility patients (n=100)

Random Allocation

Intervention group (n=50)
- Eucalyptus

Control group (n=50)
- Placebo

Measurement of Clinical Pulmonary Infection Score (CPIS) for early (Up to 96 hours from the time of airway intubation) and delay VAP (after 96 hours)

100 patients completed the study and were included in data analysis (0 Withdrawal)

Figure 1
Flow diagram of study selection and data collection process

Supplementary Files
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CONSORT-2010-Checklist-BANE-D-18-00517.docx