Original Article

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TANAFFOS

Impact of Rose Water Mouthwash on Prevention of Ventilator-Associated Pneumonia in Intensive Care Unit: A Randomized Controlled Trial

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Background: Preventing Ventilator-Associated Pneumonia (VAP) is an important strategy to increase the quality of provided care for patients under mechanical ventilation. Rose water is the main product of *Rosa damascena* which is a popular medicinal plant and has been widely used in alternative medicine. It has antibacterial activity against gram-negative and gram-positive bacteria which can potentially cause VAP.

Materials and Methods: This study was a randomized, controlled, single-center trial. 88 patients in a 21-bed surgical Intensive Care Unit (ICU) who were under mechanical ventilation met the inclusion criteria, and 80 patients fulfilled the study. Based on receiving either rose water and chlorhexidine solution or chlorhexidine solution alone, the patients were divided into two groups of control and intervention. The incidence of VAP up to 14 days was the primary outcome. Duration of mechanical ventilation, the ICU length of stay, and mortality in ICU were the secondary outcomes.

Results: There was no significant difference in demographic data, the incidence of VAP, the incidence of late-onset VAP, mechanical ventilation days, length of the ICU stay, and mortality between the two groups. However, the incidence of early-onset VAP in the intervention group was significantly lower than in the control group (p= 0.021).

Conclusion: Rose water mouthwash significantly reduced the risk of early-onset VAP without any effect on late-onset VAP.

Keywords: Nosocomial infections; Clinical trial; *Rosa damascena*; Medicinal plants

INTRODUCTION

Ventilator-associated pneumonia (VAP) is an important and common complaint in the intensive care unit (ICU) (1,2). VAP is the most common and fatal infection in ICU (3,4). This ICU-acquired infection develops after at least 48 hours of endotracheal intubation (5). Prevention of VAP is a vital strategy to increase the quality of care provided to patients under mechanical ventilation (6). More than half of the antibiotic treatments in ICU are due to VAP (7). The most important cause of VAP is oropharyngeal microorganism colonization in the upper respiratory tract (8). Antibiotic prophylaxis has unfortunately caused antibiotic resistance (9, 10).

It is ideal to find an alternative method to eliminate harmful microorganisms without producing antibiotic resistance. Chlorhexidine is the most common antiseptic agent which is used for infection prophylaxis (11, 12).

Some studies have shown that chlorhexidine care cannot efficiently reduce oropharyngeal bacterial colonization in critically ill patients, or may cause adverse effects (13, 14). On the other hand, chlorhexidine is suspected of changing the composition of oral biofilm and its metabolic activity (15). Therefore, there is an urgent need for more effective prophylaxis to prevent VAP, as well as finding a method with less complication to eliminate harmful microorganisms.

Several medicinal plant species have shown antibacterial and antifungal effects (16). Furthermore, medicinal plants possess appropriate therapeutic effects along with lower side effects (17). *Rosa damascena* Mill. (*R. damascena*) is one of the popular medicinal plants, and rose water is its main product. Rose water is a colorless liquid with a specific and pleasant odor. It is produced from the petals by the hydro-distillation method. It contains some oxygenated constituents such as benzene ethanol (18). Rose water has also been used in traditional Iranian medicine (Persian Medicine). Avicenna, an Iranian physician of the 10th and 11th centuries, used it for many medical purposes (19). Rose water has several pharmacological effects such as sedative, analgesic, anti-inflammatory, antioxidant, antitussive, antidiabetic, and antimicrobial effects (20, 21). It has a broad-spectrum antibacterial activity against gram-negative as well as gram-positive bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (20, 22). The mentioned microorganisms are the most common causes of VAP. Therefore, the goal of this study was to investigate the protective effect of rose water on VAP prevention.

MATERIALS AND METHODS

Material

Rose water samples were purchased from the supplying centers in Kashan. Chlorhexidine was purchased from Iran Najo pharmaceutical company.

Study design

This study was a randomized single-center clinical trial. The project was approved by the ethics committee of Zanjan University of Medical Science, Zanjan, Iran (approval number: IR.ZUMS.REC.1393.160). Patients admitted to the ICU were enrolled. The study was conducted in a 21-bed surgical intensive care unit in the tertiary health care institute at the university-affiliated teaching center, Mousavi educational hospital. The trial was registered with the Iranian Registry of Clinical Trials (IRCT201512115363N8). In addition, written informed consent was obtained from all the patient's relatives.

Patient population

The sample size was 40 per group considering P1 = 0.20 (proportion with VAP in the intervention group), P2 = 0.40 (proportion with VAP in the control group), $\alpha = 0.05$, $\beta = 0.20$ based on the formula of comparing two proportions.

Rose water

Rose water samples were purchased from the supplying centers in Kashan. The concentration of the essential oil detected after a liquid-liquid extraction using n-pentane as an extracting solvent .The sample was transferred to the separating funnel and sodium chloride was added. N-pentane was added and stirred. Produced gases were released. Then it remained for two hours and the oil and water phases were separated. The essential oil was in the oily phase. The oil phase of n-pentane was evaporated at 45°C and the remaining essential oil was weighed.

Inclusion criteria

A convenience sample was taken from all patients who were on mechanical ventilation for more than 48 hours. Other inclusion criteria were as follows: age between 20 to 50 years, admission less than 24 h to ICU, tracheal intubation via oral route for less than 12 h, patients who have teeth, patients who do not take any medication, the satisfaction of patients and their families, absence of any infection, diabetes, lung and heart diseases, and patients who did not receive antibiotics.

Exclusion criteria

Patients were excluded from the analysis for the following reasons: less than 7 days of admission to

hospital, pneumonia or sepsis in less than 72 h after inclusion, extubation in less than 72 h after inclusion, death in less than 72 h after inclusion, patients with contraindications for enteral feeding during the study, the unwillingness of patient's relatives to participate in this clinical trial.

Randomization and blinding

Patients who met the inclusion criteria were randomly assigned to the intervention or control group (1:1). Patients of the intervention group received 10 ml of rose water and 10 ml of 0.12% chlorhexidine oral solution as a mouthwash three times per day. The control group was given only a 10 ml oral solution of chlorhexidine of the same percentage as mouthwash three times per day. All sides of mouth were washed with chlorohexidine or rose water by a sponge swab. All patients received their mouthwash at 8 am, 2 pm, and 8 pm by four trained nurses. They had a low level of consciousness because they were sedated by fentanyl and midazolam. If their level of consciousness was not low enough to tolerate mouth washing, 2 mg of midazolam was also administrated.

According to the randomization code list, the patients were randomly allocated by block assignment between the two groups (in this method, the researcher creates 4 blocks based on the number of groups).

Clinical assessments

Patient's demographic data including age and gender, as well as Acute Physiology and Chronic Health Evaluation (APACHE) II score, were recorded at the time of admission. In this study, the Clinical Pulmonary Infection Score (CPIS) was measured every three days by a resident of anesthesiology, who was not aware of the group allocation. CPIS was based on the signs and symptoms of pneumonia, such as fever and extent of oxygenation impairment (23). CPIS score higher than 6 is defined as a positive score for VAP. CPIS has a sensitivity of 77 % and a specificity of 42 % (24). Patients were followed up for a minimum of one week and a maximum of two weeks, from the first day of admission to the ICU.

VAP definition

The diagnosis of VAP was established when a new or progressive pulmonary infiltrate existed. Two or more of the following criteria were required: (a) body temperature of <36 °C or 38 °C≤, (b) leukocytosis (>12 × 109/L) or leukopenia (<3.5 × 109/L), (c) purulent pulmonary secretions, and (d) a new or persistent pulmonary infiltration in chest radiography.

Specimens of the patients were collected and confirmed by microbiological tests. The values of broncho alveolar lavage ≥104 CFU/mL or endotracheal aspirate ≥106 CFU/mL were considered positive (25). The occurrence of VAP was recorded until extubation within a maximum period of 14 days. It was differentiated between early-onset VAP (more than 2 and less than 5 days after intubation) and late-onset VAP (more than 5 days after intubation) (26).

Outcomes

The following variables were taken from each patient: the incidence of VAP up to 14 days as the primary outcome; duration of mechanical ventilation, the ICU length of stay, and mortality in ICU were the secondary outcomes.

Safety assessment of the patients

All patients in the intervention group were assessed for the safety of the rose water consumption. Any unpleasant condition such as mucosal irritation, dryness, or allergies was considered for the safety assessment.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of quantitative variables. The values were reported as number (%) or mean ± standard deviation (SD), according to the results. The data were compared by the Kruskal-Wallis or Student t-test for continuous variables and by the chi-square or Fisher exact test for categorical variables. SPSS PC version 16.0 computer software program was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). A P value of less than 0.05 was considered significant.

RESULTS

Rose water analysis

Calculations of essential oil concentration showed that 31 milligrams of rose oil were present in every 100 milliliters of rose water (310 ppm).

Safety results

The patients of the intervention group did not report any significant local or systemic adverse effects in comparison with the control group. Moreover, the patients tolerated the rose water very well.

Patient characteristics

In total, 88 patients were assessed in this randomized trial; two patients were not included in the study due to pneumonia, and three patients due to receiving antibiotics. Out of 83 patients, 42 were in the intervention group and 41 patients in the control group. Two patients in the intervention group did not receive allocated intervention: one of them due to sepsis in less than 72 hours after inclusion and anotherone due to extubation in less than 72 hours after inclusion. One of the patients in the control group did not receive allocated intervention due to death in less than 72 hours after inclusion.

The total number of patients who received the allocated intervention was 80 including 49 males and 31 females. (Figure 1). No statistically significant difference was observed between the intervention and control groups in terms of age, gender, indication for intubation, and APACHE II score at baseline (Table 1).

Outcomes

The statistical analysis showed no significant difference between the two groups in the incidence of VAP, the incidence of late-onset VAP, mechanical ventilation days, length of the ICU stay, and mortality in ICU regarding rose water consumption during 14 days. But, the incidence of early-onset VAP in the intervention group was significantly lower than in the control group (p= 0.021). (Table 2).

Table 1. Baseline characteristics of patients who were mechanically ventilated

Variables	Intervention group (n=40)	Control group (n=40)	P Value
Age, year, mean (±SD)	45.75 (±13.12)	45.99(±12.23)	0.144*
Male, N (%)	24(60)	25(62.5)	0.515†
APACHE II score, (points) mean (±SD)	18.25(±0.77)	19.37(±0.74)	0.312 *

Control group: chlorhexidine mouthwash consumers

Intervention group: chlorhexidine and rose water mouthwash consumers

Statistical test which was used: * independent samples t-test and † Chi square. A P value<0.05 was considered significant. The abbreviation which is used, APACHE II: Acute Physiology and Chronic Health II.

Table 2. Outcome of the included patients who were mechanically ventilated

Outcomes	Intervention group (n=40)	Control group (n=40)	P value
Incidence of VAP, N (%)	6(15)	11(27.5)	0.273*
Incidence of early-onset VAP, N (%)	1 (2.5)	5 (12.5)	0.021†
Incidence of late-onset VAP, N (%)	5(12.5)	6(15)	0.153†
Duration of mechanical ventilation, days, mean (±SD)	17.1(±3)	17.9(±4)	0.622‡
Length of ICU stay, days, mean(±SD)	18.85(±14)	20.4(±11)	0.393‡
ICU mortality, N (%)	5(12.5)	10(25)	0.515*

Control group: chlorhexidine mouthwash consumers

Intervention group: chlorhexidine and rose water mouthwash consumers

Statistical test which was used: * Chi square † Fisher exact test, ‡ independent sample t-test. . A P value<0.05 was considered significant. The abbreviation which are used, ICU: Intensive Care Unit, VAP: Ventilator-associated pneumonia; Early-onset VAP: occurring between 2-5 days of mechanical ventilation, Late-onset pneumonia: occurring>5 days of mechanical ventilation.

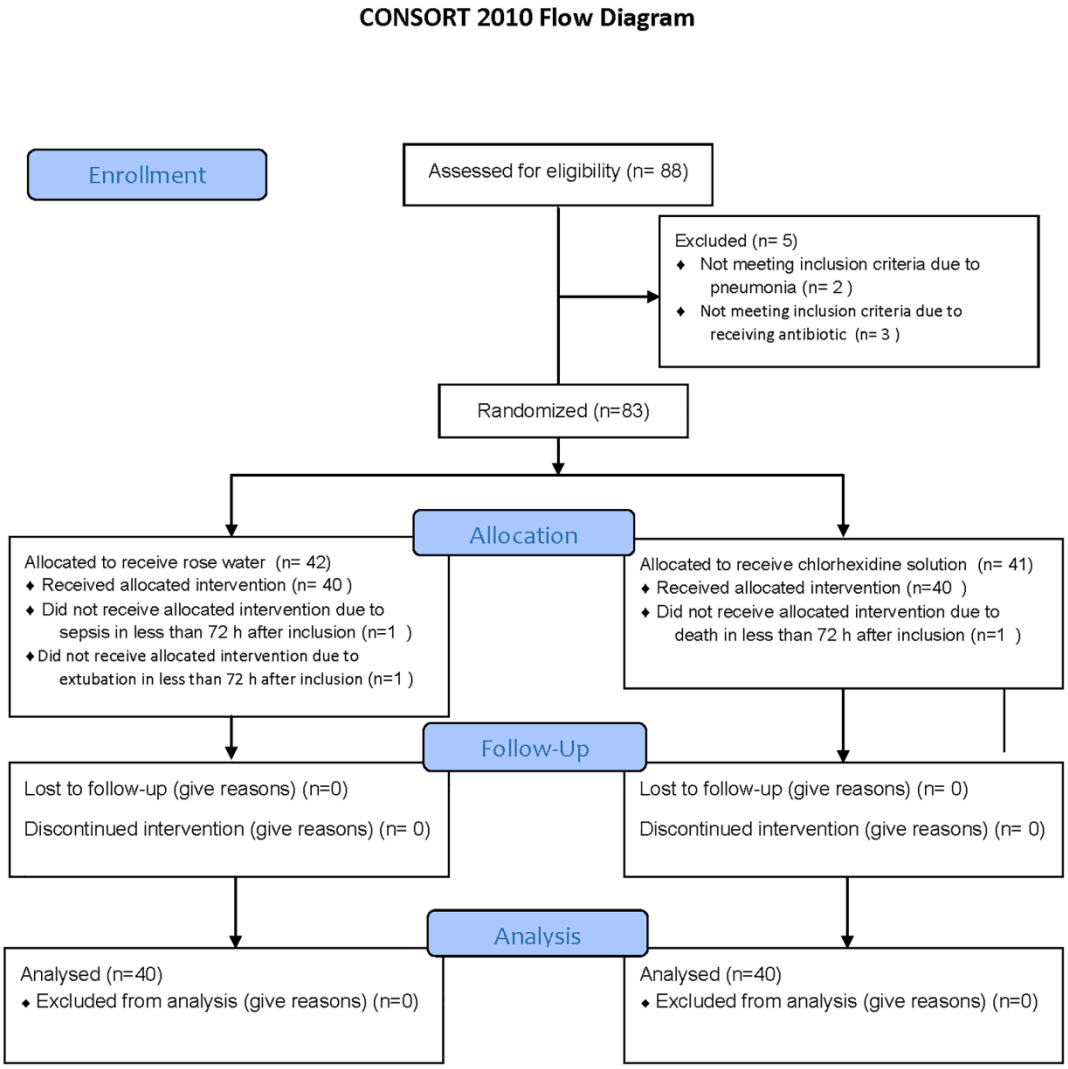

Figure 1. Consort flow diagram of the study

DISCUSSION

Many traditional medicine researchers have investigated the antimicrobial effect of the plants and their derivatives (27). *R. damascena* is one of the most important species of the Rosaceae family in Iran (28). It is commonly known as Damask rose and has many medicinal properties such as cooling, soothing, astringent, anti-inflammatory, cardiotonic, antibacterial, antimicrobial, and anti-HIV effects (29, 30). Based on the antimicrobial effect of *R. damascena*, this study was designed to determine the effect of the aromatic water of *R. damascena* as a mouthwash in the prevention of VAP. Since VAP is an important cause of morbidity in patients who are admitted to ICU, it is beneficial to prevent it in order to reduce its adverse effects on the care of these patients. We found that *R. damascena* aromatic water is effective in the prevention of early-onset VAP. According to our findings, this is the first clinical trial to examine the role of rose water mouthwash in the prevention of VAP. So, comparing our results with previous studies would be difficult.

A number of previous studies had proved the antimicrobial effect of *R. damascena* products and some other herbal mouthwashes like *Matricaria chamomilla* and *Salvadora persica*, showing an antibacterial effect in

mechanically ventilated patients (14). Fahimi et al showed that *R. damascena* extract has antibacterial activity against *Staphylococcus aureus* in a burn wound model in rats (31). Ghavam et al. had shown a broad-spectrum antimicrobial activity of *R. damascena* against gram-positive, gram-negative, acid-fast bacteria, and fungi species (32). Besides, rose water mouthwash has antibacterial activity against *Streptococcus mutans* and *Streptococcus sobrinus* (33).

Although the actual incidence of VAP is challenging to determine, VAP occurrence is estimated between 9%–27% in patients who received mechanical ventilation in the previous studies. The incidence of VAP is defined as the primary outcome that is a common complication in patients who are on mechanical ventilation. The incidence of VAP is dependent to many factors such as age, gender, duration of mechanical ventilation, the cause of hospitalization, and having chronic diseases (1, 2). In this study, the VAP incidence in the intervention group was significantly reduced by using rose water mouthwash in the early-onset VAP patients. But, rose water had no effect on the VAP incidence in the late-onset VAP or VAP. The reason could be related to different etiologic pathogens that cause early and late-onset VAP.

Susceptible bacteria to antibiotics are more dominant in early-onset VAP than late-onset VAP (34). Early-onset VAP pathogens are more antibiotic-sensitive in comparison to late-onset VAP. These pathogens are endogenous community flora, whereas pathogens responsible for late-onset VAP originate from flora modified by prior hospitalization and/or antimicrobial treatment (35). These different pathogens can explain the reason for the diverse activity of rose water mouthwash in the prevention of the two types of VAP and antibiotic-sensitive pathogens are more susceptible to rose water.

Another reason of significant different results for early and late-onset VAP may be attributed to the distinct mechanisms of rose water. Rose water has shown different mechanisms of bactericidal, bacterial growth inhibition, and bacterial biofilm formation prevention. Rose water can decrease the adhesion of bacteria, but cannot eliminate the formed biofilms (33). On the other hand, biofilm flora of the oral cavity is the source of pathogenic bacteria that can cause VAP (36). It can be concluded that rose water has interfered with biofilm formation in early-onset VAP, whereas had no effect on late-onset VAP.

In this study, patients of the intervention and control group were not significantly different in other outcomes like the length of ICU stay, the duration of mechanical ventilation, and mortality. This finding was predictable, based on the fact that the mortality and length of ICU stay were more prevalent in the late-onset VAP condition while the rose water was ineffective in late-onset VAP incidence (37).

It is worthy to note that our limitations in this study were heterogeneity in critically ill patients and differences in the cause of their hospitalization, which may influence the outcome of this study. The further important fact is that the research was carried out in a single center. So, the sample size was small.

According to our findings, this study was the first research that investigated the efficacy of rose water mouthwash in the prevention of VAP in critically ill patients. Furthermore, in this study, we tried to design the clinical trial, the methods of analysis, as well as a valid interpretation, considering the limitations.

CONCLUSION

The results of this study suggested that rose water mouthwash reduces the occurrence of VAP; however, it has only a significant effect on early-onset VAP. These findings indicate that rose water could be a useful mouthwash for preventing VAP in critically ill patients. However, it is important to consider the use of rose water for patients who suffer VAP in the early days of intubation.

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