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The Impact of Chlorhexidine Mucoadhesive Gel in the Prevention of Ventilator-Associated Pneumonia: A Randomized Clinical Trial

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ABSTRACT

Objective: Ventilator-associated pneumonia is the common cause of morbidity and mortality in the intensive care unit. Due to the antimicrobial effect of chlorhexidine, and the long-lasting result of mucoadhesive drugs, this study aimed to determine the effect of chlorhexidine mucoadhesive gel on the prevention of ventilator-associated pneumonia in critical patients.
Method: In this clinical trial, 64 ventilated patients were selected and randomly allocated into two groups. The first group received 0.2% chlorhexidine mucoadhesive gel and the second group received 0.2% chlorhexidine solution as a mouthwash. Every three days, the incidence of ventilator-associated pneumonia was evaluated by the clinical score of pulmonary infection. The data were analyzed by SPSS statistical software version 20.
Results: There was no statistically significant difference in demographic characteristics between the two groups. In the control group, 25% of the patients had ventilator-associated pneumonia, while it was only 15.6% in the intervention group; however, the incidence of ventilator-associated pneumonia revealed no significant difference between the two groups (HR ratio, 0.86; 95% confidence interval, 0.49 to 1.83 p=0.356).In addition, there was no statistically significant difference between the number of days connected to the ventilator (p=0.854), the number of days hospitalized in the intensive care unit (p=0.423), and the death rate (p=0.634) between the two groups.
Conclusion: Although no significant statistical difference was detected between chlorhexidine mucoadhesive gel and chlorhexidine solution in the prevention of ventilator-associated pneumonia, the incidence of pneumonia in the mucoadhesive gel group was clinically less than in the control group. It is better to repeat the study with a larger statistical population.

Keywords: Pneumonia; Ventilator-associated; Chlorhexidine; Mucoadhesive; Prevention.

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Introduction

Nosocomial infection is an important problem in medical centers and is one of the common and important causes of increased length of hospital stay, hospital costs, and patient deaths [1]. Among these, ventilator-associated pneumonia (VAP) accounts for 22% of these infections and is associated with a mortality rate of 20% to 50% [2, 3]. It is a subgroup of hospital-acquired pneumonia that occurs 48 to 72 hours after endotracheal intubation in patients. The tracheal tube increases the risk of VAP due to the entry of bacteria into the lower respiratory tract and the presence of factors such as reduced level of consciousness, open and dry mouth, and microaspiration of secretions [4].

Chlorhexidine (CHX) is a bisbiguanide disinfectant that is effective against a wide range of bacteria, some fungi, and some viruses, and no microbial resistance or carcinogenic effects have been reported for it [5]. Many studies have shown the positive effect of chlorhexidine on reducing VAP. However, VAP is still the most common cause of death in the intensive care unit [6]. Therefore, it is necessary to create new methods to prevent VAP.

Many pharmaceutical studies have been conducted on the formulation of drugs to increase the duration of their therapeutic effect in the oral cavity. The production of mucoadhesive drugs serves this purpose well. [7, 8] Hence, in this study, we decided to increase the presence of chlorhexidine in the oral cavity with the help of mucus-adhesive gel and investigate its effect in preventing VAP.

Materials and Methods

This study was a randomized single-center clinical trial. The project was approved by the ethics committee of Zanjan University of Medical Sciences, Zanjan, Iran (approval number: IR. ZUMS.REC.1394.224. 64 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, Mousavi educational hospital. The trial was registered with the Iranian Registry of Clinical Trials (IRCT201602095363N9). Valid informed written consent was obtained from all the patient's relatives. These patients had previously been divided into two groups by random allocation method. Patients were randomly allocated by block assignment in two groups according to statistician randomization code list. The first group was the intervention group, in which 5 cc of mucoadhesive gel containing 0.2% chlorhexidine was used as a mouthwash three times a day. The second group was considered the control group, in which a mouthwash of 0.2% chlorhexidine oral solution was used in the amount of 5cc three times a day.

Patient population:

The sample size was 32 per group based on P1=0.414 (proportion with VAP in the intervention group), P2=0.688 (proportion with VAP in the control group), α=0.05, β=0.20 based on the formula of comparing two proportions. The power of the study was 80%.

Chlorhexidine mucoadhesive gel preparation:

The gelling solution was obtained from carbomer and hydroxypropyl cellulose (HPC) by dissolving different amounts of each polymer in distilled water. To prepare 100cc of the desired gel, first, 3 grams of HPC were added to the volume of 50 cc distilled water. Then, 1 cc of 20% chlorhexidine mouthwash was added to it. 0.4 grams of carbomer was brought to volume of 50cc with distilled water. The obtained solutions were mixed for 15 minutes at 1000 rpm. The pH of the obtained gel was brought to 7 by the appropriate amount of NaOH. The final concentrations in the obtained gel were 3% hydroxypropyl cellulose, 0.4% carbomer, and 0.2% chlorhexidine.

Inclusion criteria were: patients who were on mechanical ventilation for more than 48 hours; age between 20 and 50 years old; admission of less than 24 hours in intensive care unit; Tracheal intubation via oral route for less than 12 hours; patients who have teeth; patients who do not take any medication before admission; patient's relatives consent; absence of any infection, diabetes, lung and heart diseases; patients who did not receive antibiotics.

Exclusion criteria were: less than 7 days' admission to the hospital; Pneumonia or sepsis less than 72 hours after inclusion; Extubation less than 72 hours after inclusion; death less than 72 hours after inclusion; patients with contraindications to any cause of enteral feeding during study; unwillingness of patient's relatives to participate in this study.

Randomization and Blinding

Patients who met the inclusion criteria were randomly assigned to the control or intervention group (1:1). The first group was the intervention group, in which 5 cc of mucoadhesive gel containing 0.2% chlorhexidine was used as mouthwash three times a day. The second group was the control group, which used 5 cc of the oral solution containing 0.2% chlorhexidine three times a day as a mouthwash. According to the study statistician randomization code list, the patients were allocated randomly by block assignment between the two groups (in this method, the researcher creates 4 blocks based on the number of groups in 2 groups).

In this assessor-blinded study, participants were blinded to their assigned study group. The researcher, who studied the variables, did not know the groups of the study, and another person was responsible for the mouthwashes used for the patients.

Clinical Assessments

Patient demographic data, including age, gender,

history of antibiotic use, the reason for intubation, and the reason for admission to the intensive care unit and Acute Physiology and Chronic Health Evaluation (APACHE) were collected at the time of admission. In this study, the Clinical Pulmonary Infection Score (CPIS) was measured every three days by an anesthesiology resident who was unaware of the intervention and control group. CPIS calculations included variables such as the number of white blood cells, oxygenation rate, radiographic information, and examination of samples taken from the trachea [9]. A CPIS score higher than 6 was defined as a positive score for VAP [10]. 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

VAP diagnosis was established when a new or progressive pulmonary infiltrate existed. Two or more of the following criteria were required: (a) body temperature (<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 infiltrate on chest radiography.

Specimens of all 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.

Outcomes

The following variables were taken from each patient: VAP incidence was measured every three days up to 12 days as the primary outcome. Duration of mechanical ventilation, the ICU length of stay, and mortality in the ICU were the secondary outcomes. All secondary outcomes were recorded at the end of the study, which included patients' discharge or death.

Statistical Analysis

After completing the information collection checklists, the data were analyzed by SPSS PC version 20 computer software program for all the statistical analyses (SPSS Inc., Chicago, IL, USA). 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 Student t-test for continuous variables and by the chi-square or Fisher exact test for categorical variables. A p value of less than 0.05 was considered significant.

Results

Patient Characteristics

In total, 72 patients were included in this study, of which 5 people were excluded due to taking antibiotics and 3 people due to lack of satisfaction. Of the 64 enrolled patients, 32 were entered to the chlorhexidine mucoadhesive gel group (intervention group) and 32 entered the chlorhexidine solution group (control group) (Figure 1).

In terms of gender, there were 38 men (59.3%) and 26 women (40.6%) in this study. According to the results obtained from the chi-square test, no significant difference was observed in terms of gender between the two groups (Table 1).

The average age of the patients was 38.89±12.37 years. Statistically, there was no significant difference between ages in the two groups (Table 1).

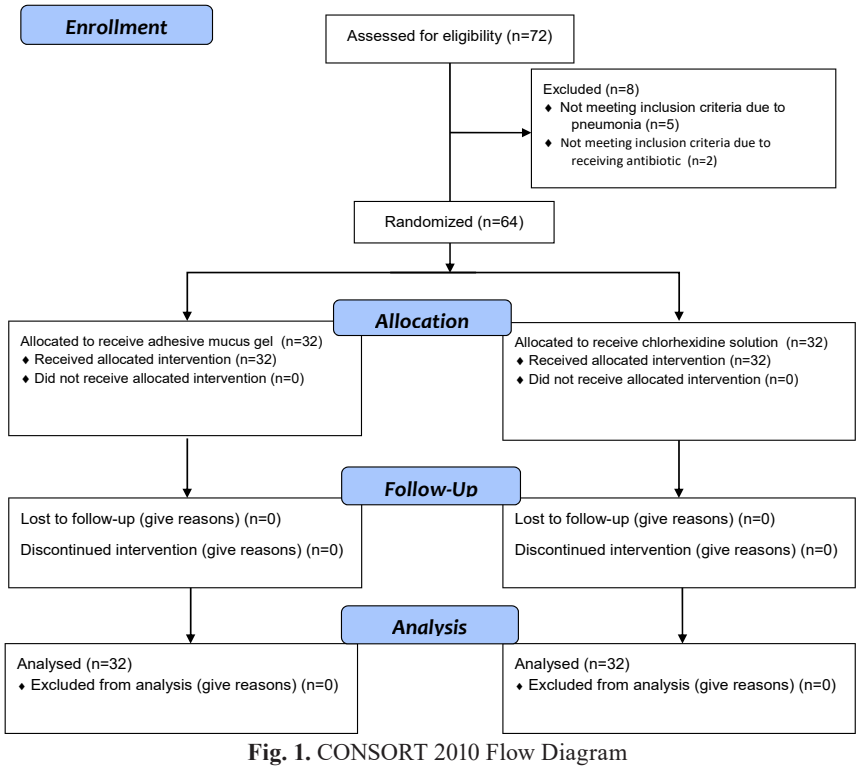

Fig. 1. CONSORT 2010 Flow Diagram

Table 1. Demographic characteristics of patients

		Chlorhexidine mucoadhesive gel group (n=32)	Chlorhexidine solution group (n=32)
Male, n (%) †	Male	20 (62.5%)	18 (56.2%)
Age, n (%) *	20 to 29 years	5 (15.6)	7 (21.8)
	30 to 39 years	11 (34.37)	12 (37.5)
	40 to 49 years	16 (50)	13 (40.6)
Reason for hospitalization in the intensive care unit, n (%)†	Multiple trauma	16 (50)	15 (46.8)
	Non-traumatic cerebral hemorrhage	3 (9.3)	5 (15.6)
	Brain tumor	2 (6.2)	2 (6.2)
	Other causes	11 (34.3)	10 (31.25)
APACHE II, mean±SD*		18.12±0.82	18.90±0.86

Statistical tests used: * Independent sample t-test and † Chi-square. *p* value<0.05 was considered significant. APACHE II: Acute Physiology and Chronic Health II

Table 2. Outcomes of patients in the two study groups

	Chlorhexidine mucoadhesive gel group (n=32)	Chlorhexidine solution group (n=32)	*p* value
Ventilator-associated pneumonia incidence rate, number (%)	5 (15.62)	8(25)	0.356*
Number of days connected to the ventilator, mean±SD	15.3±7	16.8±4	0.854†
Number of days hospitalized in the intensive care unit, mean±SD	18.9±7	19.6±6	0.423†
Mortality rate in the intensive care unit, number (%)	5 (15.62)	7 (21.87)	0.634*

Statistical tests used: * Chi-square, †Independent sample t-test. *p* value<0.05 was considered significant

Out of the 64 examined patients, 31 patients were due to multiple trauma, 8 were due to non-traumatic cerebral hemorrhage, 4 were due to brain tumors, and 21 were due to other causes (mesenteric ischemia, femoral fracture, rectal cancer, etc.) and were hospitalized in the intensive care unit. According to the results obtained from the chi-square test, there was no significant difference in the causes of hospitalization between the two groups, statistically (Table 1).

The range of APACHE II score in 64 patients was 22-16 and the average APACHE II score in 64 patients was 18.81. Statistically, there was no significant difference between the two groups (Table 1).

Outcomes

The statistical analysis showed no significant difference between the two groups in the incidence of VAP, which was the primary outcome group (HR ratio, 0.86; 95% confidence interval, 0.49 to 1.83 p=0.356) between the two groups. Also, there was no statistically significant difference in secondary outcomes including mechanical ventilation days, length of the ICU stays, and mortality in ICU between the two groups (Table 2).

The effect size of the number of days connected to the ventilator and the number of days hospitalized in the intensive care unit was 0.2 and 0.1, respectively.

Discussion

In this study, for the first time, we used the chlorhexidine mucoadhesive form for the prevention of VAP and compared it with the traditional forms of mouthwash in patients admitted to the intensive care unit. The results of this study showed that the incidence of pneumonia, the number of days connected to the ventilator, the number of days hospitalized in the intensive care unit, and mortality were not statistically significant between the two groups.

Recently, there have been many challenges to provide an effective way to prevent VAP. Some studies have shown that chlorhexidine care cannot efficiently reduce bacterial oropharyngeal colonization in critically ill patients [11, 12]. It would be ideal to find a method that can more effectively eliminate the harmful microorganisms involved in VAP [13, 14]. Our results showed that the incidence of pneumonia in the mucoadhesive gel treatment group was 15.6% and the incidence of pneumonia in the chlorhexidine solution mouthwash treatment group was 25% clinically (5 cases of pneumonia in the adhesive group and 8 cases in the normal mouthwash group). Although in the chlorhexidine mucoadhesive gel group, the incidence of pneumonia was lower (nearly 10%) than in the control group, this result was not statistically significant. Chlorhexidine is gradually released due to its cationic properties and high adhesion to most areas of the mouth [15]. The slow-release form of chlorhexidine and its mucoadhesive properties, which were used in this study in the form of a mucus-adhesive gel, may have increased the contact time of this bactericidal substance and could explain these reasons.

In this study, patients in the intervention and control groups did not have significantly different lengths of ICU stay or durations of mechanical ventilation. A similar finding was noted by Veitz-Keenan et al.

in which they suggested that chlorhexidine in ICU patients has no significant effect on the length of ICU stay or the duration of mechanical ventilation [16].

Several studies have been done in order to identify the factors that increase death among patients admitted to ICUs [17]. Although the mortality rate did not decrease statistically in the intervention group, the mortality rate decreased clinically. As a result, it can be claimed that if the study is conducted in a multi-centered manner with a large sample size, VAP and mortality in patients admitted to the intensive care unit would be significantly reduced. In previous studies, a direct relationship between the reduction of mortality and pneumonia has been shown, which is consistent with the recent study [18].

Polymers have been used in past studies to prevent ventilator-associated pneumonia. Jones et al.have used coating polyvinyl chloride endotracheal tubes with hydrogels to entrap nebulized antimicrobial solutions for the prevention of VAP [19]. Carbomers and HPC are widely used in food and cosmetic products and so far, no allergic, inflammatory, or toxic reactions have been recorded in humans and animals in consumed doses [20, 21]. In the present study, all patients in the intervention group were assessed for the safety of chlorhexidine mucoadhesive gel. Any unpleasant condition such as mucosal irritation, dryness, and allergies were not considered in any of the patients.

The present study had numerous limitations. This investigation was a single-center study with a low sample size, which might reduce the trial findings' generalizability (external validity, applicability). In addition, a low sample size can reduce the power of the study in discovering differences and finding relationships. The present study had several strengths. This research for the first time studied the mucoadhesive form of chlorhexidine for the prevention of ventilator-associated pneumonia in the intensive care unit. Therefore, its results can be a basis for conducting more extensive studies. Although chlorhexidine mucoadhesive gel did not have an advantage over routine chlorhexidine mouthwash statistically, the incidence of pneumonia in the mucoadhesive gel users was clinically lower than in the control group. Although the use of mucoadhesive gel in this research was not statistically superior to chlorhexidine mouthwash in reducing VAP, more investigations with a larger statistical population are recommended.

Declaration

Ethical considerations: The present study was approved by the ethics committee of Zanjan University of Medical Sciences with the ethics code ZUMS.REC.1394.224, which has been registered in the Iran Clinical Trials Registration Center with the code IRCT201602095363N9. Informed consent was obtained from the patients' families before the start of the study.

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Conflict of interest: There is no conflict of interest in this research.

Authors' contributions: TN and FD designed and conducted this study. AZ helped in the data analysis and interpretation of the results. FD prepared the manuscript.

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