ORIGINAL PAPER

doi: 10.5455/medarh.2018.72.206-209
MED ARCH. 2018 JUN; 72(3): 206-209
RECEIVED: MAR 10, 2018 | ACCEPTED: MAY 15, 2018

Evaluating the Efficacy of Nanosil Mouthwash on the Preventing Pulmonary Infection in Intensive Care Unit: a Randomized Clinical Trial

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ABSTRACT

Introduction: Oral and Oropharynx colonization and Micro-aspiration of discharges are two important processes in ventilator-associated pneumonia (VAP). So, this study design to investigated the preventive effect of oral decontamination program by Nanosil mouthwash on incidence of ventilator-associated pneumonia. **Methods:** 80 newly hospitalized patients who admitted in intensive care unit (ICU) of Amin Medical Education Center were enrolled to a randomized clinical trial study. Patients were randomly divided into two equal groups. In the intervention group, a multi-stage oral decontamination program was performed by using Nanosil mouthwash three times a day, and in the control group oral decontamination was performed by Chlorhexidine 0.12% with same method. The oral decontamination program was continuing for five days. The VAP was diagnosed with a version of modified clinical pulmonary infection scale (MCPIS) on the first and fifth days. **Results:** In compare the case and control groups, there wasn't observed significant difference in age, gender, underling disease, smoking, and primary mean scores of MCPIS, sequential organ failure assessment (SOFA) and Glasgow coma scale (GCS) ($P>0.05$). In the both groups, the mean scores of SOFA and GCS were significantly improve in fifth day ($P<0.05$). After five days follow up, the mean score of MCPIS (1.2 ± 0.1 *vs.* 3.5 ± 0.3, $P<0.001$) and pneumonia rate (2.7% vs. 23.7%, $P=0.008$) were significantly lower in case group. But, the mortality rate was same in both groups ($P>0.05$). **Discussion:** The use of oral care program with Nanosil mouthwash is better than Chlorhexidine for the prevention of VAP in patients who admitted in ICU.

Keywords: Nanosil, Mouthwash, Intensive Care Unit, Ventilator Associated Pneumonia.

1. INTRODUCTION

Hospital infections are one of the major and common challenges in healthcare centers and causes of prolonged hospitalization, increased patients morbidity and mortality and medical costs (1). Ventilator-associated pneumonia (VAP) is one of the most important subgroups of nosocomial infections. The incidence of VAP was 10-20% in the first 48-72 hours after endotracheal intubation and mechanical ventilation (2, 3). Also, VAP is responsible of 27-47% of infections in ICU and its associated risk of death is estimated 33-50% (4, 5).

The endotracheal intubation disturbed cough and swallowing reflexes and causes mucus accumulation in the oral cavity and accelerates bacterial proliferation (6). Also, bacterial proliferation was exacerbated in oral and nasal cavity due to immune system dysfunction during 24 hours after admission to the ICU. In the following, these secretions and bacterial colonies migrate to the lower respiratory tract near the endotracheal tube and can finally leads to pneumonia (7). So, the center for disease control and prevention (CDC) offer the oral hygiene as a best strategy for prevention of VAP (3).

Two major component of Nanosil mouthwashes are hydrogen peroxide and few silver ions. Hydrogen peroxide destroyed bacterial and viral protective membranes and therefore prevents anaerobic bacterial proliferation (8). Silver ions Binds to bacterial proteins with extremely firm covalent bonds and causing bacterial deactivation (9-12). Both hydrogen peroxide and silver ions have synergistic effects (9).

So far, chlorhexidine has been considered as a golden standard for oral hygiene in patients with mechanical ventilator. On base of several studies, chlorhexidine reduced oral bacterial colonization (13-16) and thereby re-

ducing pneumonia incidence rate (3). However, recently some studies have shown that the Nanosil mouthwashes has comparable effect with chlorhexidine to prevent bacterial colonization in vitro (9, 12). Therefore, Given the importance of oral hygiene in preventing VAP, this study design to compare the efficacy of Nanosil and chlorhexidine Mouthwashes for preventing ventilator-associated pneumonia in patients who admitted in ICU.

2. METHODS AND MATERIALS

The present study is a randomized clinical trial study (Iranian Registry of Clinical Trials Number of: IRCT2017091636194N1) with the case and control groups. The statistical population of research included newly hospitalized patients in the intensive care unit of Amin hospital of Isfahan University of Medical sciences (Iran) from November 2016 to May 2017.

The criteria of entering the study have been the age between 18 to 70 years old, lack of clear trauma to the jaw and face that prevents oral care, having tracheal tube, locating the patient under mechanical ventilation, lack of pneumonia or respiratory infections at the beginning of entry to the hospital (MCPIS <7) up to 48 hours after intubation and there is no ban in respect of using Nanosil or Chlorhexidine such as allergy. Of the 97 patients, 80 patients on base of entry criteria were enrolled in this study and randomly divided into two equal groups.

Measurement tools

The SOFA instrument is one of the disease severity assessment tools that evaluates the function of six vital organs including respiratory system by measuring PO2/FiO2 ratio, cardiovascular system by measuring main arterial presser and the need for blood pressure boosters, coagulation system by measuring platelet levels, liver function by measuring total bilirubin levels, nervous system by measuring Glasgow scale and renal system with measuring urine output and creatinine level. These scores are evaluated in one 24-hour period. The score for each system is between 0 to 4 and the total score is between the 0 to 24. Organ dysfunction and organ failure characterized with scores of 1-2 and 3-4, respectively (17).

Glasgow Coma Scale (GCS) is a measure for determining the severity of alertness in people over the age of 5 years. The GCS consists of three parts; the first part involves opening the eyes with 4 scores, the second part is the verbal answer with 5 scores and the third part is the movement response with 6 points. The maximum and minimum GCS score is 15 and 3, respectively. If the patient was intubated, there is no possibility to check the verbal answer, and therefore at least score was 2T and a maximum score was 10T (18). The modified clinical pulmonary infection score (MCPIS) was calculated by evaluation of tracheal secretions (Rare=0, Abundant=1, Abundant + purulent=2), Chest X-ray infiltrates (no infiltrate=0, diffused=1, localized=2), Temperature (36.5-38.4=0, 38.5-38.9=1, >39 or <36=2), Leukocytes count, per mm3 (4,000 -11,000=0, < 4,000 or > 11,000=1, < 4,000 or > 11,000 + band forms 500=2), PAO2/FIO2, mmHg (> 240 or ARDS=0, 240 and no evidence of ARDS=2) and microbiology (negative=0, positive=2). the minimum and maximum scores of MCPIS were 0 and 12, respectively. MCPIS over than 7 was diagnostic for VAP (19).

Study design and data collection

Then, patient's primary data included age, gender, underling disease and history of smoking was recorded. Before the intervention, GCS, SOFA and MCPIS score were calculated for all patients in case and control groups.

Patients in the control group received standard treatment. For this patients, oral care was done by 15 mL of a 2% chlorhexidine solution, 3 times per day for five days that involved brushing the teeth, suctioning oral secretions, and rubbing the oropharyngeal mucosa. Patients in case group received oral care with same method except that Nanosil was used instead of chlorhexidine. The intervention continued for five days or until obtaining the exit criteria (death, extubation, transfer to other wards and performing any diagnostic and therapeutic procedures in the oral and throat areas).

Five days after initiation of intubation, the incidence of pneumonia was measured again by MCPIS instrument in both the case and control groups. Also, the GCS and SOFA scores were calculated and the frequency of pneumonia incidence was recorded in the end of study.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and good clinical practice according to the International Conference on Harmonization guidelines. The study was approved by ethics committee of Isfahan University of Medical Sciences and registered in Iranian Registry of Clinical Trials with number of IRCT2017091636194N1.

Data Analysis

After collecting data, data was analyzed by SPSS software version 18. To compare qualitative data, the chi-square test and Fisher's exact test were used as appropriate. The t-test was used to analyze quantitative data. Also, the probability of mortality rate was calculated by Mann-Whitney and Wilcoxon test. P value less than 0.05 was considered statistically significant.

3. RESULTS

Of the 97 patients, 80 patients were enrolled in this study and randomly divided into two equal groups. During the study, 3 patients in the case group and 2 patients in the control group were excluded. Finally, data of 37 patients in the case group and 38 patients in the control group were analyzed (Figure 1).

There was no significant statistical difference between the mean age in the two groups and they were equal in respect of age (41.6±15.9 *vs.* 44.1±16.5, P=0.49). 67.5 percent of samples in the control group and 72.5 percent of samples in the case group were male (P=0.63). In the control group, 30 percent and in the case group 35 percent of the patients had cigarette addiction (P=0.63). Also, the frequency of underling disease were 37.5% and 45% in the control and case groups, respectively (P=0.50). the mean score of SOFA, GCS and MCPIS were given in Table 1. As you can see, there is no statistically significant difference between the two groups in the

Variables		Case Group	Control Group	P value
Age (Mean±SD)		41.6±15.9	44.1±16.5	0.49
Gender	Male (%)	29 (72.5%)	27 (67.5%)	0.63
	Female (%)	11 (27.5%)	13 (32.5%)	
Underling disease (%)		22 (55%)	25 (62.5%)	0.50
Smoking (%)		14 (35%)	12 (30%)	0.63
MCPIS (Mean±SD)		1.4±0.2	1.1±0.2	0.31
SOFA (Mean±SD)		7.5±2.4	7.3±2.5	0.75
GCS (Mean±SD)		5.0±1.7	5.1±1.7	0.90

Table 1. Compare patient's Primary data. MCPIS: Modified Clinical Pulmonary Infection Scale, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale

Variables	Case Group	Control Group	P value
MCPIS (Mean±SD)	1.2±0.1	3.5±0.3	<0.001
SOFA (Mean±SD)	6.7±2.5	6.3±2.8	0.50
GCS (Mean±SD)	7.0±2.1	6.8±2.03	0.70
Pneumonia (%)	1 (2.7%)	9 (23.7%)	0.008

Table 2. Compare the mean of MCPIS, SOFA, GCS and frequency of pneumonia in fifth Day. MCPIS: Modified Clinical Pulmonary Infection Scale, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale

Time	Probability of mortality	Case group frequency (%)	Control group frequency (%)	Z	P
First day	0-10%	21 (52.5%)	16 (40%)	1.02	0.31
	15-20%	13 (32.5%)	17 (42.5%)		
	40-50%	6 (15%)	6 (15%)		
	50-60%	0	0		
Fifth day	0-10%	26 (70.3%)	23 (60.5%)	0.74	0.46
	15-20%	7 (18.9%)	12 (31.6%)		
	40-50%	4 (10.8%)	1 (2.6%)		
	50-60%	0	2 (5.3%)		
Wilcoxon test	Z	1.99	2.19	-	

Table 3. Frequency distribution of mortality rate in two groups on the first and fifth day of intervention

mean scores of SOFA, GCS and MCPIS (Table 1). In the fifth days, there were not observed significant difference in the mean score of SOFA (6.7±2.5 *vs.* 6.3±2.8, P=0.50) and GCS (7.0±2.1 *vs.* 6.8±2.03, P=0.70) between case and control groups. But, MCPIS score was significantly higher in control group (3.5±0.3 *vs.* 1.2±0.1, P<0.001) (Table 2). Also, paired t-test showed that the mean score of MCPIS in the case group did not show significant difference between the two times (P=0.54). But, paired t-test showed that the mean score of MCPIS in the control group on the fifth day of study were significantly higher than the first day of study (P <0.001). For all patients in case and control groups, the mean score of SOFA and GCS was significantly improve after the five days follow up (P<0.05). Ventilation association pneumonia were observed in 1 patient of case group (2.7%) and 9 patients of control group (23.7%). Oral care with Nanosil solution significantly better than Chlorhexidine reduced the incidence of ventilation association pneumonia (P=0.008) (Table 2). Finally, the Mann-Whitney test showed that there was no significant difference between the two groups in the mortality rate on the first and fifth day of study (P> 0.05). Wilcoxon test showed that the mortality rate in both groups on fifth day was significantly lower than the first day (P <0.05) (Table 3).

4. DISCUSSION

VAP is the most commonly diagnosed infectious disease in Intensive Care Unit (20, 21). The incidence of this complication varies according to hospitals and facilities and is reported to be between 13 and 51 people per 1,000 ventilators per day (22). VAP is associated with prolonged hospitalization (23), longer mechanical ventilation (24), increased hospital costs and a doubling of the risk of death (25). CDC recommend oral hygiene as the best preventing strategy for VAP (3). Therefore, finding more effective mouthwash can reduce the incidence of VAP. The results of our study indicated that the both of Nanosil mouthwash and Chlorhexidine mouthwash reduced the risk of VAP. However, Nanosil mouthwash was more effective than Chlorhexidine and dramatically save the MCPIS score and reduced the incidence of VAP.

In a study by Meinberg et al. in 2012 in the intensive care unit, 28 patients were treated with 2 percent Chlorhexidine gel, brushing teeth 4 times a day, and 24 patients were also treated with placebo gel with brushing 4 times a day. The results of their study also showed no statistically significant difference between the results of the two groups, as well as the ineffectiveness of Clorhexidine mouthwash (26). In the study of Lorente et al., benefited from a high statistical size, 217 patients were under oral care with Chlorhexidine gel of 0.12 percent with brushing three times a day, and 219 patients were also under oral care with only Chlorhexidine gel of 0.12 percent three times a day. The results showed that there was no statistically significant difference between the two groups in terms of pneumonia reduction (27). In a systematic review study conducted by El-Rabbany et al. in 2015, they investigated 28 performed researches about Chlorhexidine and the impact of oral health on the prevention of pneumonia. The results of their investigation showed that the role of Chlorhexidine is still debatable and requires greater studies for confirmation (28).

So far, no clinical studies have compared the efficacy of Nanosil and Chlorhexidine mouthwashes on preventing VAP. In a laboratory study conducted by Kariminik et al., they investigated the effect of Chlorhexidine and Nanosil mouthwashes and some antibiotics on streptococcus mutans bacterium isolated from dental plaque in a laboratory environment. The results of their study showed that this bacterium and most of its products have most susceptibility to Nanosil mouthwash (12). Isfahanian et al. study was conducted for the laboratory comparison of the antibacterial effect of two mouthwashes of Nanosil and Chlorhexidine; in this laboratory-comparative study the sampling of supragingival and subgingival plaques of 15 patients was done, and the number of bacteria was determined in two aerobic and anaerobic fluid environments by spectrophotometer. The results concerning Chlorhexidine showed that there was no significant difference between cultivated colonies in both aerobic and anaerobic environments, but in the case of

Nanosil mouthwash, the number of developed colonies, especially in the anaerobic environment, has been severely reduced (9). The lesser effect of Chlorhexidine in the present study may be due to this principle that this substance has a small antimicrobial spectrum. In other words, Chlorhexidine primarily affects Gram-positive organisms, while Gram-negative microbes are the most common organisms in the oral-pharyngeal cavity of critically ill patients (29). Whereas, Nanosil component such as hydrogen peroxide and silver ions by destroyed bacterial and viral protective membranes and bacterial inactivation have a broad spectrum antibacterial effect (8-12). Our results confirm the previous in-vitro studies that shown the Nanosil mouthwash has a stronger antibacterial effect on oral bacteria (9, 12).

5. CONCLUSION

The results of this study showed that Nanosil is more effective than Chlorhexidine in the prevention of VAP occurrence, and its reduces VAP incidence in critically ill patients hospitalized in the intensive care units.

- **Acknowledgments:** We are grateful to official members of ICU departments of Amin Hospital for their help.
- **Author's Contribution:** Bahareh Khaky, Ahmadreza Yazdannik and Hosein Mahjoubipour contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.
- **Conflict of interest:** none declared.

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