

Comparison of the Effect of Chlorhexidine Mouthwash with Matrika Mouthwash Drop on Probable Ventilator-associated Pneumonia in Intensive Care Unit

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Background: Daily use of Chlorhexidine mouthwash following endotracheal intubation is done routinely in intensive care units (ICU). Matrika (Chamomile extract) has shown antibiotic activities, and several articles report it has similar preventive effect as Chlorhexidine on ventilator associated pneumonia, and also on oral cavity hygiene. Our study aimed to compare rate of VAP occurrence in two groups of intubated patients receiving Chlorhexidine and Matrika in Alzahra hospital's ICU.

Methods: In this trial 90 ICU patients who were intubated endotracheally, were randomly divided into two groups who will receive one of Chlorhexidine (group A) or Matrika (group B) mouthwash every 8 hours. Occurrence of VAP was determined in the following 5 days after intubation, using the standard VAP diagnosis criterion.

Results: 8 of 45 (17%) patients experienced VAP in the first five days after intubation in the Chlorhexidine group, and, 9 of 45 (20%) patients in the Matrika group experienced the same condition. VAP rate was not significantly lower in the Chlorhexidine group (p value= 0.73).

Conclusion: The results show that VAP occurs in Chlorhexidine and Matrika group approximately at a similar rate. Our findings recommend further studies on Matrika as an alternative to Chlorhexidine.

Keywords: Ventilator associated pneumonia; Chlorhexidine mouthwash; Matrika mouthwash; Intensive care unit

Nowadays the daily use of Chlorhexidine mouthwash following endotracheal intubation is done routinely in Intensive care units (ICU) [1]. That's because researchers consider improvement of oral hygiene as the most important method in prevention of Ventilator associated pneumonia (VAP), by inhibition of oral flora colonization [2-3]. Nosocomial infections, including pneumonia, are of the most important causes of death in ICUs [4]. VAP is a type of nosocomial pneumonia that occurs after 48 hours of mechanical ventilation, and is a regular and serious problem among these ICU patients [5-6]. VAP occurs in 9-27% of intubated patients, and leads to death in 20-70% of VAP cases [7]. Chlorhexidine is a detergent which effects on wide spectrums of microorganisms [8]. Mouthwashing with Chlorhexidine has decreased the rate of VAP in many studies [9-13], however it didn't show that effect in some other studies [14-16]. It has been recommended to design studies which evaluate other methods of VAP prevention and oral hygiene providing [17]. Matrika is an herbal alcohol based

mouthwash and detergent extracted from *Matricaria Chamomilla*. It has anti-inflammatory, antioxidant, antiseptic, antiviral, pain killing, and wound healing effects [18-19]. Considering less side effects, herbal mouthwashes are a probable alternative to Chlorhexidine [20]. In this study we did a comparison on the effect of Chlorhexidine and Matrika mouthwash in preventing VAP.

Methods

We conducted a prospective double blind randomized study for 90 intubated patients in AL-Zahra hospital's ICU, in Esfahan, between 2017-2018.

Patients from two ICUs in the hospital were divided into 2 groups. The first group (Group A, or the Chlorhexidine group) received mouth washing by 10ml of 0.2% Chlorhexidine solution every 8 hours. The second group (Group B, or the Matrika group) received mouthwash using 25 drops of Matrika in 10ml of normal saline every 8 hours as follows. For mouthwash an abaisse-langue, covered with sterile gauze sank in the solution, then the whole mouth and its organs were washed with it.

Inclusion criteria:

Age more than 18 years, –needing mechanical ventilation for at least 48 hours, –no use of endotracheal tube before admission to ICU, –no antibiotic therapy in 2 months before the admission –natural teeth, –consenting to participate in the study by the patient, or, his/her guardians.

Exclusion criteria:

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Not consenting to be in the study, –pregnancy, –immune deficiency, –overt lesion in mouth or near to the mouth.

Measurement:

Demographic variables such as age, sex, and smoking were recorded and compared between the two groups. Related clinical information including the cause of admission to the hospital, cause of ICU admission, duration of hospitalization before ICU admission, duration of hospitalization in ICU, drugs administered (in 5 groups as seen in results), duration of mechanical ventilation (with maximum of 5 days that we followed the patients) were recorded and compared between the two study groups.

Occurrence of tracheal tube cuff tearing, and administration of prokinetic agents were considered as confounder variables but were not strongly thought to influence the outcome because of the low rate of prescription.

All patients were followed for 5 days after intubation to determine occurrence of VAP. VAP was defined and diagnosed using standard criterion designed for it available on BioMed Central. Considering that ICU patients receive several drugs as a routine and knowing it is not our aim to evaluate the influence of each drug separately on VAP, we measured the drug history of patients in 5 categories, in order to provide a more accurate and medically relevant history of the patients to rule out the effect of underlying diseases.

Ethical considerations:

The ethical and scientific contents of the study was approved by research ethics committee in Isfahan University of Medical Sciences.

Statistical analysis:

The sample size was calculated based on previous studies such as Munro's [9]: 40 patients. We conducted the study on 45 patients. Patients after obtaining consent were allocated to study groups by Random Allocation program. Data was imported to SPSS-23 program and analyzed. In order to report quantitative variables mean \pm SD and in order to report qualitative variables the percentage was reported. In order to

compare qualitative variables between the two groups sample T-test was used. The plan was to use Mann–Whitney test when the data was not normally distributed, and if needed, to use Fisher's exact test. P value <0.05 was defined as significant.

Results

90 patients in 2 groups of 45 patients were included. 52 (57%) of the patients were male, and 38 (43%) were females. There wasn't a significant difference between Chlorhexidine group and Matrika group in the gender ratios (p value = 0.18) and also no significant difference was seen between the 2 groups in positive history of smoking, 17 (37%) patients in Group A and 18 (40%) in group B (p value = 0.807). The average of age was 59.18 years (\pm 20.15) in Chlorhexidine group and 60.78 (\pm 18.41) years in Matrika group, which shows no significant difference (p value = 0.69).

As seen in the table 1, duration of hospitalization before referring the patients to ICU had an average of 19.42 (\pm 22.392) hours in the Chlorhexidine group and 14.78 (\pm 22.761) hours in Matrika group which shows no significant difference (p value = 0.952). Also, the duration of hospitalization in ICU could be measured in most of the cases and did not show significant difference between the two groups of our study. It had an average of 34.94 (\pm 39.004) days in the Chlorhexidine group and 41.33 (\pm 43.010) days in Matrika group (p value = 0.429). As table 1 shows, we did not see significant difference between the two groups in needing and receiving the 5 drug categories of drugs including Micro nutrition (p value = 0.777), antibiotics (p value = 0.591), Albumin (p value = 0.663), Insulin (p value = 0.340), and Anti-Hypertension drugs (p value = 0.673). There was no significant difference between Chlorhexidine group and Matrika Group in the cause of hospital admission of patients (p value = 0.94). Also, in the causes of referring the patients to the ICUs of the hospital no significant difference was seen (p value = 0.91). More information about the variables can be seen in the (Table 1).

Table 1- Demographic variables and clinical information; drugs administered and cause of hospital admission

Characteristics	Groups		P Value
	Chlorhexidine (Group A)	Matrika (Group B)	
Demographic variables			
Age (year)	59.18 \pm 20.15	60.78 \pm 18.41	0.69
Sex (M/F)	25/20 (55/45%)	27/18 (60/40%)	0.67
Smoking	17 (37%)	18 (40%)	0.807
Clinical information			
Time before ICU (hours)	19.42 (\pm 22.392)	14.78 (\pm 22.761)	0.332
Time in ICU (days)	34.94 (\pm 39.004)	41.33 (\pm 43.010)	0.514
Drugs administered			
Micro nutrition	38 (84%)	37 (82%)	0.777
Antibiotic	32 (71%)	31 (68%)	0.591
Albumin	22 (48%)	20 (44%)	0.663

Table 1- Demographic variables and clinical information; drugs administered and cause of hospital admission (Continued)

Characteristics	Groups		P Value
	Chlorhexidine (Group A)	Matrika (Group B)	
Insulin	14 (31%)	10 (22%)	0.340
Anti-Hypertension	22 (48%)	24 (53%)	0.673
Cause of hospital admission			
Loss of consciousness and low GCS	6 (13%)	7 (15%)	
Lower limbs weakness	3 (6%)	2 (4%)	
Head and neck trauma	5 (11%)	5 (11%)	
Multiple trauma	10 (22%)	9 (20%)	
Dyspnea	4 (8%)	3 (6%)	0.94
Elective surgery	5 (11%)	7 (15%)	
Abdominal pain	1 (2%)	3 (6%)	
Bone fractures	3 (6%)	1 (2%)	
Progressive weakness	2 (4%)	4 (8%)	
GI complaints	4 (8%)	2 (4%)	
Headache	2 (4%)	2 (4%)	
Cause of ICU admission			
Cerebro-vascular accident	7 (15%)	6 (13%)	
Meningeal hemorrhage	3 (6%)	5 (11%)	
Unstable condition following surgery	7 (15%)	6 (13%)	
Difficulty of awakening after general anesthesia	5 (11%)	6 (13%)	0.91
Intracerebral hemorrhage	2 (4%)	2 (4%)	
guillain-barré syndrome	2 (4%)	3 (6%)	
Shock	10 (22%)	5 (11%)	
Multi-organ failure	7 (15%)	8 (17%)	
Respiratory failure	2 (4%)	4 (8%)	
Confounder Variables			
Tube's cuff tearing	0	1 (2%)	0.315
Use of prokinetic	1 (2%)	1 (2%)	1.0
Study Outcome			
Ventilator Associated Pneumonia (VAP)	8 (17%)	9 (20%)	0.788
Time of Pneumonia	77.25 (\pm 21.7)	77.22 (\pm 15.7)	0.998

The confounder variables (Tube's cuff tearing, and prokinetic use) were not seen in more than one patient in the two groups of 45 patients.

Occurrence of VAP following endotracheal intubation and 48 hours of mechanical ventilation, happened in 8 of the 45 patients in the Chlorhexidine group (17.77%) and in 9 of the 45 patients in the Matrika group (20.0%) which shows no significant difference between the two groups of study (p value = 0.788). There was no significant difference between the two groups also, in time of occurrence of VAP. It had an

average of 77.25 (\pm 21.7) hours in the Chlorhexidine group and 77.22 (\pm 15.7) hours in the Matrika group (p value = 0.998).

Discussion

Kanafani et al's study showed that mouthwashing with Chlorhexidine reduces respiratory infections and reduces the need for antibiotic therapy [21]. Nicolosi et al's study reports significant reduce in VAP rate in cardiovascular surgery patients receiving mouthwashing with

Chlorhexidine [7]. It was reported by Goes and co-researchers that Chamomile (Matrika) significantly reduces gingival inflammation and plaque formation in patients undergoing orthodontic treatment with fixed appliances. It reduced biofilm accumulation and gingival bleeding in patients with gingivitis, probably because of its antimicrobial and anti-inflammatory activities [22]. Azimi and co-researchers in Iran reported that Chlorhexidine mouthwash has been more effective in prevention of colonization of bacteria within the mouth in comparison with Matrika and saline mouthwashes. However, none of the tested mouthwashes in that study (saline, Matrika, and Chlorhexidine) were able to remove *Staphylococcus Aureus*, *Pseudomonas*, *Klebsiella*, and *Acinetobacter* [23].

Because of better results, Matrika was recommended for gingivitis treatment in comparison with Chlorhexidine by Paknejad and co-researchers [24]. In another article by Atai and co-researchers, Matrika showed better antibiotic function in comparison with other herbal mouthwashes, however, all herbal mouthwashes had lower antibiotic effect when compared to Chlorhexidine group [25].

Contrary to Azimi and co-researchers' study, Matrika and Persica mouthwashes reduced *Staph. Aureus*, and *Strep Pneumonia* bacteriae significantly in Firouzian and co-researchers' study. They recommended these two mouthwashes as alternatives to Chlorhexidine in ICU care [26].

Safarabadi's study on another herbal mouthwash, Echinacea, resembled a similar efficacy of Echinacea and Chlorhexidine [27]. Gholami's study as well, showed reduction of VAP in Echinacea mouthwash group comparing to Normal Saline group, but it wasn't reported significantly lower. They recommended other studies with wider database and bigger groups [28]. Bo L's study was done to determine efficacy of probiotics in preventing studies but could not introduce it as an efficient prevention [29]. It narrows the alternatives probable for Chlorhexidine. Halm and co-researchers published an article on Oral cavity hygiene and VAP and reported that mouthwashing prior to mechanical methods of oral hygiene providing, i.e. toothbrushing [30].

Considering the studies mentioned before, Matrika shows a good antibiotic and anti-inflammation effect. It is a safe and easy-to-use mouthwash extracted from chamomile. Our results show that beside Chlorhexidine, Matrika should be in the mind of researchers in the field of ICU cares and oral hygiene. It can be a beneficial alternative to use for complicated, ill patients in ICUs which receive plenty of medications every-day.

Limitations:

Our study did include two groups with high resemblance, we could determine almost all the data we planned to record, even-though considering that most of the patients were intubated in emergency medicine and/or outside the ICU, risk of un-sterility and doing the mouthwashing with lower experience and standard went up. The 2 ICUs had Internal, Surgical, Respiratory, and Neurologic cases every-day, but we did not have the resources to investigate VAP in our cases considering every disease and survey the effects of medications, drug by drug. Another limitation to use Matrika instead of Chlorhexidine is that the staff do not know the dosage difference or some prefer to use the previous routine instead of adherence to the study's guideline.

Conclusion

The results show that VAP occurs in Chlorhexidine and Matrika group approximately at a similar rate. It is conforming to plenty of studies mentioned formerly in this article and looks clinically true according the known mechanisms of Matrika. But, Chlorhexidine is broadly used as a safe, wide spectrum, available mouthwash with no records of serious side-effects. It has no absorption through the skin or mucous membranes [31]. In contrary, other mouthwashes have not gone through years of evaluation and research and have not shown better or exactly similar effects to Chlorhexidine. To consider other mouthwashes like Matrika as an alternative to Chlorhexidine for preventing VAP, more data and multi-dimensional clinical trials are needed.

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