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Research Paper – Araştırma Makalesi

EFFECTIVENESS OF ORAL CARE SOLUTIONS TO PREVENT VAP in PATIENTS ON MECHANICAL VENTILATION: SYSTEMATIC REVIEW AND META-ANALYSIS

MEKANİK VENTİLASYON DESTEĞİNDEKİ HASTALARDA VENTİLATÖR İLİŞKİLİ PNÖMONİYİ ÖNLEMEK İÇİN KULLANILAN AĞIZ BAKIM SOLÜSYONLARININ ETKİNLİĞİ: SİSTEMATİK İNCELEME VE META-ANALİZ

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Özet

Bu araştırma mekanik ventilasyon desteğindeki hastalarda farklı ağız bakım solüsyonlarının ventilatörle ilişkili pnömoni üzerine etkisini belirlemek amacıyla yapılmıştır. Mekanik ventilasyon desteğindeki hastalarda ağız bakımı solüsyonlarının ventilatör ilişkili pnömoniyi (VİP) önlemedeki etkinliğini değerlendirmek için PubMed, EBSCO, Embase, Web of Science, Clinical Trials gibi veri tabanlarından ve Türkiye Ulusal elektronik veri tabanlarından randomize kontrollü çalışmalar tarandı. Genel olarak, 2028 taramadan elde edilen toplam 10 randomize kontrollü deneysel çalışma analize dahil edildi. Çalışmaların toplam örneklem büyüklüğü 777'dir (müdahale grubu: 417; kontrol grubu: 360). Bu meta-analizde kapsamlı ağız bakımı VİP enfeksiyonu olasılığını azaltmada etkiliydi ancak hangi çözümün daha etkili olduğu konusunda net bir sonuca varılamadı. Bu sonuçlara dayanarak, mekanik ventilasyondaki hastalarda VİP'i önlemede hangi ağız bakım çözümlerinin daha etkili olduğu konusunda bir sonuca varmak için daha güçlü kanıtlara ihtiyaç vardır.

Anahtar Kelimeler: Yoğun bakım ünitesi, meta-analiz, ağız bakımı, ağız bakım solüsyonları, ventilatör ilişkili pnömoni

Abstract

This study was conducted to determine the effect of different oral care solutions on ventilator-associated pneumonia in patients under mechanical ventilation. To evaluate the effectiveness of oral care solutions in preventing VAP in patients under mechanical ventilation, randomized controlled studies were searched from databases such as PubMed, EBSCO, Embase, Web of Science, Clinical Trials and Turkey's National electronic databases. Overall, a total of 10 randomized controlled experimental studies from 2028 scans were included in the analysis. The total sample size of the studies was 777 (intervention group: 417; control group: 360). In this meta-analysis, comprehensive oral care was effective in reducing the likelihood of VAP infection, but did not provide a clear conclusion as to which solution was more effective. Based on these results, stronger evidence is needed to reach to a conclusion about which of the oral care solutions are more effective in preventing VAP in patients on mechanical ventilation.

Keywords: Intensive care unit, meta-analysis, oral care, oral care solution, ventilator-associated pneumonia

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1. INTRODUCTION

Ventilator associated pneumonia (VAP) is an infection of the pulmonary parenchyma with a high morbidity and mortality rate, which develops minimum 48 hours after invasive mechanical ventilation and seen commonly in intubated patients. Advanced age, treatments, multiple organ failures, severe clinical condition, immobilization, endotrachael tube use, sedative and muscle relaxants administered to patient promote VAP development (Centers for Disease Control and Prevention, 2024, pp.6-19; Pozuelo-Carrascosa et al., 2020; Sharma et al., 2018, pp. 169-178). The incidence of VAP in patients on mechanical ventilation (MV) is 20 times more than that in patients who do not MV (Akca et al., 2014, pp. 742-744; Gutiérrez et al., 2019, pp. 180).

There are many pharmacological and non-pharmacological interventions to prevent VAP. One of the most important non-pharmacological nursing interventions to prevent VAP is to use correct, effective and regular oral care (Abidia, 2007, pp.1-8; Enwere et al., 2016, pp. 3; Koff et al., 2011, pp. 489-495). Nurses can provide oral care using solutions with scientifically proven efficiency to patients on MV and prevent VAP by reducing changes and bacterial colonization in the oral mucosa.

Different solutions are used for oral care to prevent VAP in patients on MV in the literature and the most commonly recommended solution is chlorhexidine gluconate solution (Coşkun et al., 2017, pp. 28-35; Güler and Türk, 2018, pp. 1-19; Zand et al., 2017, pp. 318-322). Studies on this subject in the literature report that different concentrations (0.12%, 0.2%, 1% and 2%) of chlorhexidine gluconate mouthwash were effective on microbial colonization and development of VAP (Özdemir and Türk, 2022, pp. 1-9; Tuon et. al; 2017, pp. 159-163; Zand et.al, 2017, pp. 318-322). A study reported that a significant reduction was achieved in the development of VAP when 0.12%, 0.2%, and 1% chlorhexidine solutions were used for oral care (McCue and Palmer, 2019, pp. 263-268). Zand et al. (2017, pp. 318-322) found in their study that 0.2% chlorhexidine solution was effective in preventing VAP. Tuon et al. (2017, pp. 159-163) found in their study that 2% chlorhexidine solution used for oral care was the most effective concentration in preventing development of VAP. On the other hand, use of chlorhexidine in oral care was also associated with a mortality risk in some recent studies (Deschepper, 2018, pp. 1017-1026; Klompas, et al., 2016, pp. 1277-1283; Parreco M, et al., 2020, pp. 659-664). In their meta-analysis Berry et al. (2011, pp. 686-688) reported that using sodium bicarbonate, saline and 0.12% chlorhexidine as oral care solutions did not result in a significant change in VAP incidence. Another randomized controlled trial on this subject compared sterile distilled water with listerine and sodium bicarbonate and found that listerine or sodium bicarbonate was not superior to distilled water (Berry, 2013, pp. 275-281). In their study, Tsuda et al. (2020, pp.62) found that povidone-iodine solutions inhibited bacterial growth in the oral cavities of patients on MV. However, when the literature is examined, it is rarely determined that nanosil mouthwash, LP299, miswak, ozonated water are used in oral care. (Hanifi et al., 2017, pp. 1-8; Irani et al., 2019, pp. 1-7; Khaky et al., 2018, pp. 206-209; Klarin et al., 2018, pp. 272). 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 (Ayala-Núñez et al., 2009, pp. 2-9). Silver ions binds to bacterial proteins with extremely firm covalent bonds and causing bacterial deactivation (Kariminik and Motaghi, 2015, pp. 18-21). Probiotic bacteria Lactobacillus plantarum 299 (Lp299) is a probiotic additive without any known side effects.

This strain adheres to the mucosa throughout the gastrointestinal tract, thereby enhancing its ability to withstand colonization by potential pathogens (Johansson et al., 1993, pp. 15-20; Klarin et al., 2005, pp. 285-293; Stjernquist-Desatnik et al., 2000, pp. 215-219). The Salvadora persica plant is popularly known as the miswak tree. One end of the miswak stem is cut in the form of a brush. The brush is used to clean the crevices between teeth to remove any food residue. In terms of oral health, Salvadora persica has been reported to be antibacterial, antifungal and antiplaque (Al-Ayed et al., 2016; Pribadi et al., 2014, pp. 1048-1051; Varma et al., 2018, pp. 21-27). Another mouthwash used in oral care is ozonated water. It is also effective in destroying bacteria, viruses, fungi and oral microorganisms accumulated in dental plaque, such as Streptococcus spp (Anupunpisit et al., 2004, pp. 1-2; Cesar et al., 2012, pp. 269-274).

When the studies in the literature are reviewed, sufficient evidence that proves that the most effective solution in preventing development of VAP in patients on MV cannot be found. In the studies, a variety of solutions were found to be effective in preventing VAP. Different from the other studies, this study intended to determine the effectiveness of the most effective oral care solution used to prevent VAP or reduce VAP incidence in patients on MV. We believe that the study findings can provide guidance to nurses about the use of most suitable and effective oral care solution, and prevent development of VAP which is one of the most common infections in patients on MV and thus contribute to safe patient care.

Aim and questions of the study

This study intended to determine the effectiveness of oral care solutions used to prevent development of VAP in patients on MV based on the findings of previous studies.

1.What is the effectiveness of oral care solutions used in the prevention of VAP?

2.Which of the oral care solutions used to prevent VAP is more effective?

2. MATERIALS AND METHODS

2.1. Study design

This is a systematic review and meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Check List was used to write systematic review and meta-analysis study report (Page et al., 2021, pp. 1-9). The study protocol was entered in PROSPERO database (CRD42021258772). Literature search, selection of papers, data extraction and quality assessment of the papers included in the study were independently done by two researchers under the supervision of the third researcher in order to prevent and control risk of bias in the study. Any difference of opinion on a literature study was settled through discussion sessions among all three researchers.

2.2. Inclusion and exclusion criteria

Randomized controlled trials in Turkish and English which were published between 2016 and 2022 and whose full texts were accessible were included in this study. Studies included in this systematic review and meta-analysis met the following PICOS criteria:

Study group (P): Intubated patients in intensive care unit.

Intervention (I): Oral care with oral solutions

Comparison (C): Groups receiving different oral care solutions.

Outcomes (O): VAP incidence or VAP prevalence and CPIS score (as described in the studies).

Study design (S): Randomized controlled trials conducted in healthcare institutions.

Studies with no clearly identified or understood method, studies without accessible full texts and studies with no clear VAP assessment criteria were excluded.

2.3. Data sources and search strategy

The literature search for this systematic review was conducted in July 2021 and additional searching were done on 10-15 December 2022 using the re-runnig searches method. Literature search was done on PubMed, EBSCO (Medline, CINAHL), Embase (OVID) Web of Science, PsycINFO (all via Ovid SP), ClinicalTrials and Turkey's National (Ulusal Tez Merkezi, Dergi park, Türkiye Klinikleri and TR Dizin) electronic databases. The keywords ("oral care" OR "oral hygiene" OR "topical antiseptic") AND ("ventilator associated pneumonia" OR VAP) were used for the literature search on international databases according to the Medical Subject Headings were used in national databases. Additionally reference lists of the studies included in the study and reference lists of previous reviews were checked. This systematic review included randomized controlled trials in Turkish and English which were published between 2016 and 2022. Since it is aimed to take up-to-date studies and it is a systematic review in which studies before 2016 are determined, it is limited to studies from 2016 and up to date.

2.4. Selection of studies

Potential papers which could eligible to be included in our study were selected independently by two authors by excluding repeated articles from the records of the literature search and selecting according to study title and abstract. Mendeley-Reference Management Software was used to remove duplicate records and manage the selection process of articles. Papers in Turkish and English were downloaded to allow the review of their full texts. Then all article texts were reviewed in a session with the participation of all authors and studies that could be included in the analysis were selected. Selection process of articles included in the study is shown in Figure 1.

2.5. Data extraction

A data extraction tool developed by the researchers was used to obtain the study data. Data on the study design, location and timing of the study, study methods, data sources, study sample size and properties, names of the scales used and main findings of the study was obtained using this data extraction tool. Data extraction process was carried out independently by the first and second authors under the supervision of the experienced researcher after the pilot study done with the third author and then data obtained was checked and then transformed into a single text.

2.6. Methodological quality assessment of the studies

Methodological quality of these papers included in this systematic review was assessed independently by the first two authors and checked by the experienced authors of the study.

The critical appraisal check list of Joanna Briggs Institute for randomized controlled trials was used to assess methodological quality (Tufanaru et al., 2020, pp.72-133). This tool consists of 13 questions and each question is answered as "yes, no, unclear and not applicable". Methodological quality level of a study was "mediocre quality" if less than 50% of the questions were answered with yes; "moderate quality" if 51-80% of the questions were answered with yes and "good quality" if more than 80% of the questions were answered with yes.

2.7. Data synthesis

Meta-analysis was used for data synthesis in this systematic review. Review Manager 5.4 was used for meta-analysis. Effect size was calculated by meta-analysis for each outcome variable reported in one or more studies. Heterogeneity between studies was assessed using the $\chi 2$ test and I^2 statistic. I^2 is 0-40% indicated might not be important, I^2 is 30-60% represented moderate heterogeneity, I^2 is 50%–90% represented substantial heterogeneity, and I^2 is 75-100% indicated considerable heterogeneity (Deeks et al., 2021, pp.243-296). I^2 higher than 50% was accepted as an important heterogeneity indicator in this study. Random Effect results were used if I^2 was higher than 50% and Fix Effect results were used if it is less than 50%. Odds Ratios were calculated with 95% confidence interval (CI) for categorical variable (VAP prevalence) and Mean Difference (MD) was calculated for continuous variable (CPIS score) with 95% confidence interval (CI). All tests were calculated from two-tailed tests, and a p value of less than 0.05 was considered statistically significant.

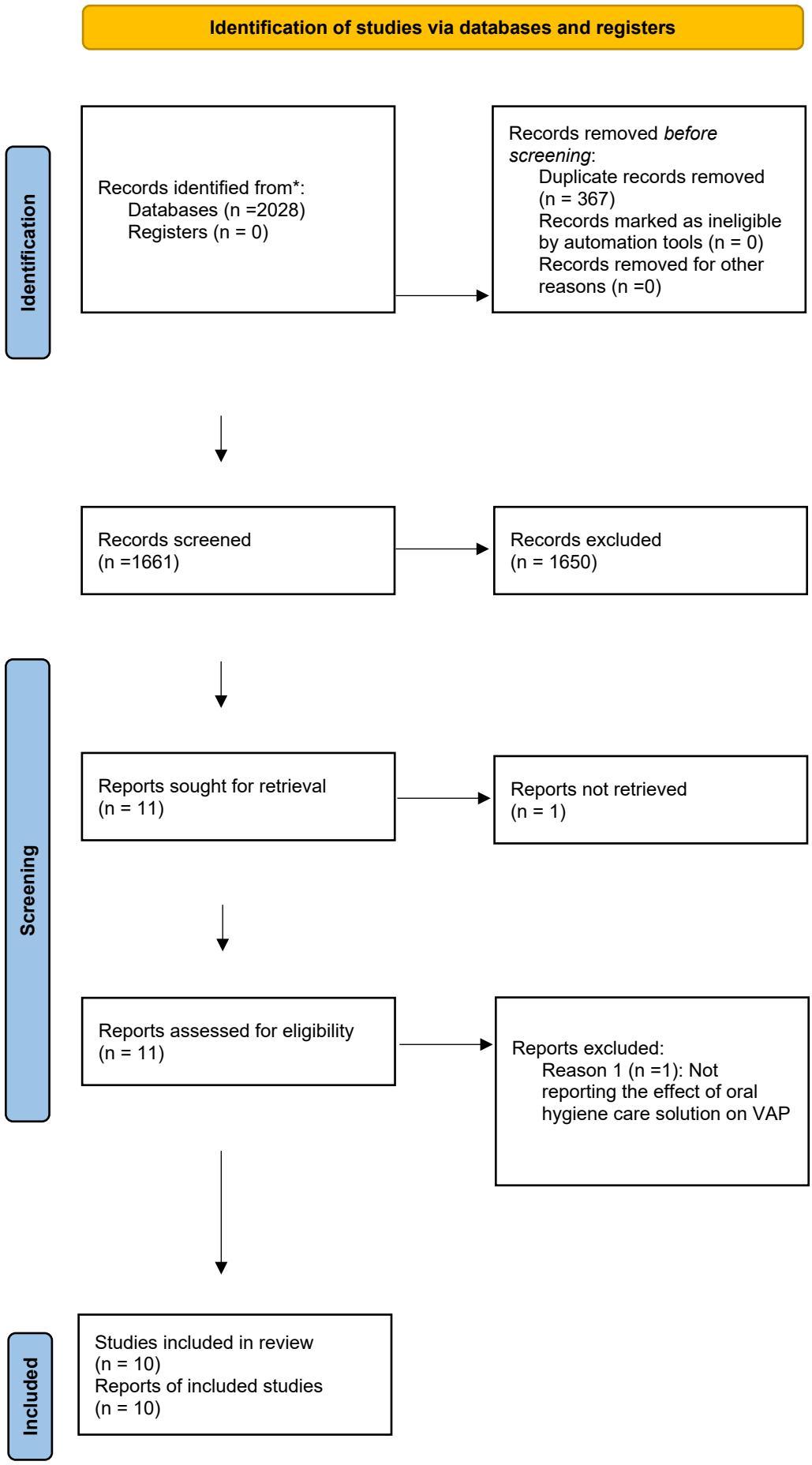
For sensitivity analysis, when a solution was compared with different solutions, a subgroup analysis was performed according to the type of solution being compared. However, in order to determine which solution was more effective in this study, network meta-analysis could not be performed because the assumptions of homogeneity, similarity, and consistency among the studies included in the systematic review could not be met (Cooper et al., 2012, pp. 32-45; Li et al., 2011; Rouse et al., 2017, pp. 103-111).

3. RESULTS

3.1. Literature search results

A total of 2028 records were found in the database search in this study. After selecting according to title and abstract with the planned search strategy and repeats were excluded, full texts of eleven studies were reviewed. One of the studies reviewed was excluded as it did not provide any VAP data and a total of 10 papers were included for analysis (Figure 1).

Figure 1: PRISMA flow diagram



3.2. Study and participant characteristics

All studies included in the systematic review are randomized controlled trials. Studies were conducted in Iran (6 studies), Turkey (2 studies), Sweden (1 study), Brazil (1 study). (Table 1). The studies included in the analysis were done between 2004 and 2020 and published between 2016 and 2022. The total sample size of the studies was 777 (intervention group: 417; control group: 360). Data collection tools, age and group characteristics of participants in the studies are shown in Table 1.

Table 1: Characteristics and Results of the Trials Included in the Systematic Review, Which Used Oral Care Solutions

Authors (year) / Country	Study design	Intervention	VAP diagnosis tool	Study year	Sample size	Mean age, year (SD)	Main results
Kes et al. 2021 / Turkey	RCT	0.12% CHX group Placebo group: sodium bicarbonate	CPIS	2019-2020	CHX group: 29 Placebo group: 28	The mean (SD) age of patients in the placebo group: 77.37 (10.1) 0.12% CHX group: 72.79 (12.0) years	VAP 0.12% CHX group: 10 (34.5) Placebo group: 17 (60.7)
Irani et al. 2019 / Iran	RCT	Control group: 0.2% CHX The intervention Group: miswak	MCPIS	2018	Intervention group: 35 Control group: 35	The intervention (miswak) group: (33.65±13.50) Control (chlorhexidine) group (34.83 ± 13.95)	VAP Intervention group: 0 (0%) Control group: 6 (17.1%)
Kaya et al. 2018 / Turkey	RCT	Study group: 5% glutamine, Control group: 2% CHX solution.	CPIS	2014-2015	Study group: 44 Control group: 44	Control group 48.57 ± 17.36 Study group was 50.93 ± 15.18.	Control group CPIS score: 4.07±1.78 Study group CPIS score was 3.78±2.25
Khaky et al. 2018 / Iran	RCT	Case group: Nanosil Mouthwash Control group: 2% CHX	MCPIS	2016 - 2017	Case Group: 40 Control Group: 40	Case Group: 41.6±15.9 Control Group: 44.1±16.5 (18 – 70)	VAP Case Group: 1 (2.7%) Control Group: 9 (23.7%)
Klarin et al. 2018 / Sweden	RCT	Lp299 group Control group: 0.1% CHX	Respiratory parameters Lung Injury Score Blood gas analysis CRP and white blood cell counts Parenteral/enteral administration of drugs and fluids Nutrition and total volumes Vomiting and gastric residual volumes	2004–2007	Lp299 group: 31 Control group: 29	Lp299 group: 66 (57–76) Control group: 65.5 (53.75–75)	VAP Lp299 group: 7 Control group: 10

Meidani et al. 2018 / Iran	RCT	0.2 % CHX group 0.01 Potassium permanganate group Control group: placebo	CDC	2011-2012	0.2 % chlorhexidine: 50 0.01 Potassium permanganate : 50 Control group: 50	Control group: 51.7±18.9 CHX group: 50.6±19.1 Permanganate group: 49.8±22.7	VAP Control group: 15 (30%) Chlorhexidine group: 6 (12%) Permanganate group: 7 (14%)
Hanifi et al. 2017 / Iran	RCT	Experimental group: ozonated water Control group: 0.2% CHX	CPIS	2013-2014	Experimental group: 39 Control group: 35	Experimental group: 44.42 ± 1.39 Control group: 44.61 ± 1.78	VAP Experimental group: 6 (14.6%) Control group: 14 (30.6%)
Tuon et al. 2017 / Brazil	RCT	CHX group: 2% CHX placebo group: 0.9% NaCl	CDC	2014-2015	CHX group: 8 Placebo group: 8	CHX group: 53.1 years Placebo group: 42.8 years	VAP CHX group: 4 Placebo group: 2
Zand et al. 2017 / Iran	RCT	0.2% CHX group 2% CHX group	CPIS	During the 5-month study period	0.2% CHX group: 57 2% CHX group: 57	0.2% CHX group: 45.43 ± 2.95 2% CHX group: 44.45 ± 2.72	VAP 0.2% CHX group: 13 (22.8%) 2% CHX group: 3 (5.3%)
Nobahar et al. 2016 / Iran	RCT	The intervention Group: 3% HP Control group: 0.9% normal saline (NS)	MCPIS	May 23rd and December 23rd, 2013	Intervention group: 34 Control group: 34	Intervention group: 66 ± 15.5 Control group: 63.4 ± 20.5	VAP Intervention group: 5 (14.7%) Control group: 13 (38.2%)

RCT: Randomized Controlled Trial. MCPIS: Modified Clinical Pulmonary Infection Score. CPIS: Clinical Pneumonia Infection Score. VAP: Ventilator-associated pneumonia. CHX: Chlorhexidine. HP: Hydrogen Peroxide. NS: Normal Saline. CDC: Centres for Disease Control and Prevention.

3.3. Quality assessment results

The quality assessment level was moderate in five randomized controlled trials and good in five randomized controlled trials (Table 2).

Table 2: Quality Assessment Scores of the Studies

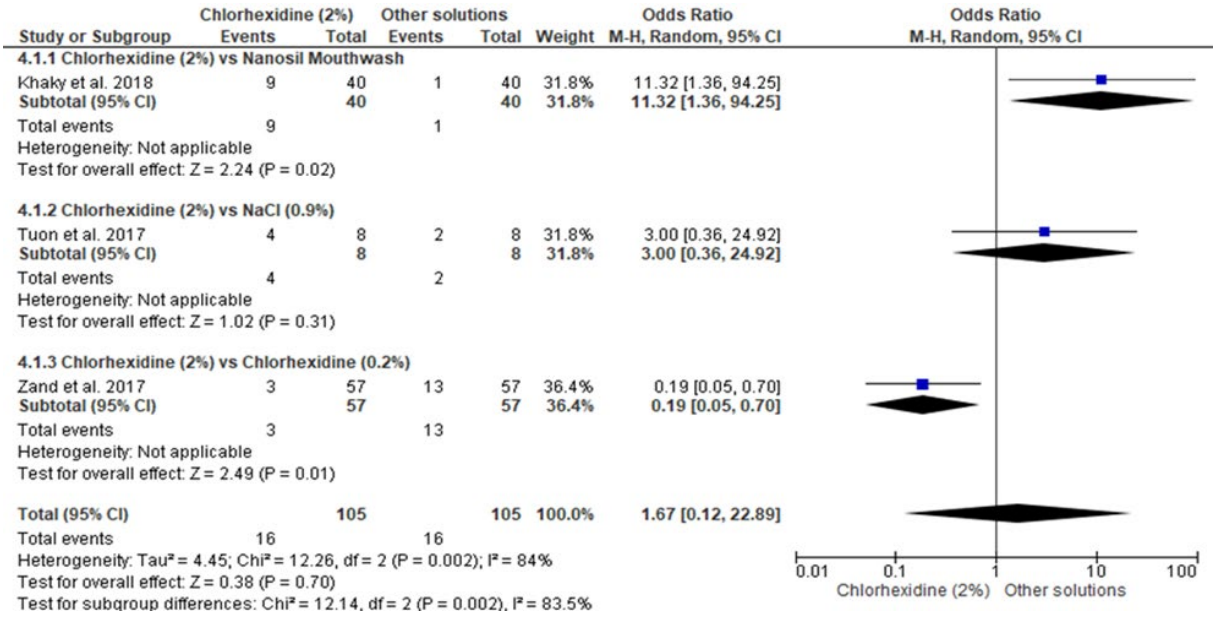
Studies	JBI critical appraisal check list questions for randomized controlled trials													Quality scores of the studies
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	
Kes et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Good quality (92%)
Irani et al. 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Good quality (92%)
Kaya et al. 2018	Y	U	Y	Y	N	U	Y	Y	Y	Y	Y	Y	N	Moderate quality (69%)
Khaky et al. 2018	Y	U	Y	Y	U	N	Y	Y	Y	Y	Y	Y	N	Moderate quality (62%)
Klarin et al. 2018	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Moderate quality (77%)
Meidani et al. 2018	N	U	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	N	Moderate quality (69%)
Hanifi et al. 2017	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	N	Good quality (85%)
Tuon et al. 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Good quality (85%)
Zand et al. 2017	Y	U	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Moderate quality (54%)
Nobahar et al. 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Good quality (85%)

Q: Question Y: Yes N: No, N/A: Not applicable; U: Unclear

3.4. Meta-analysis results

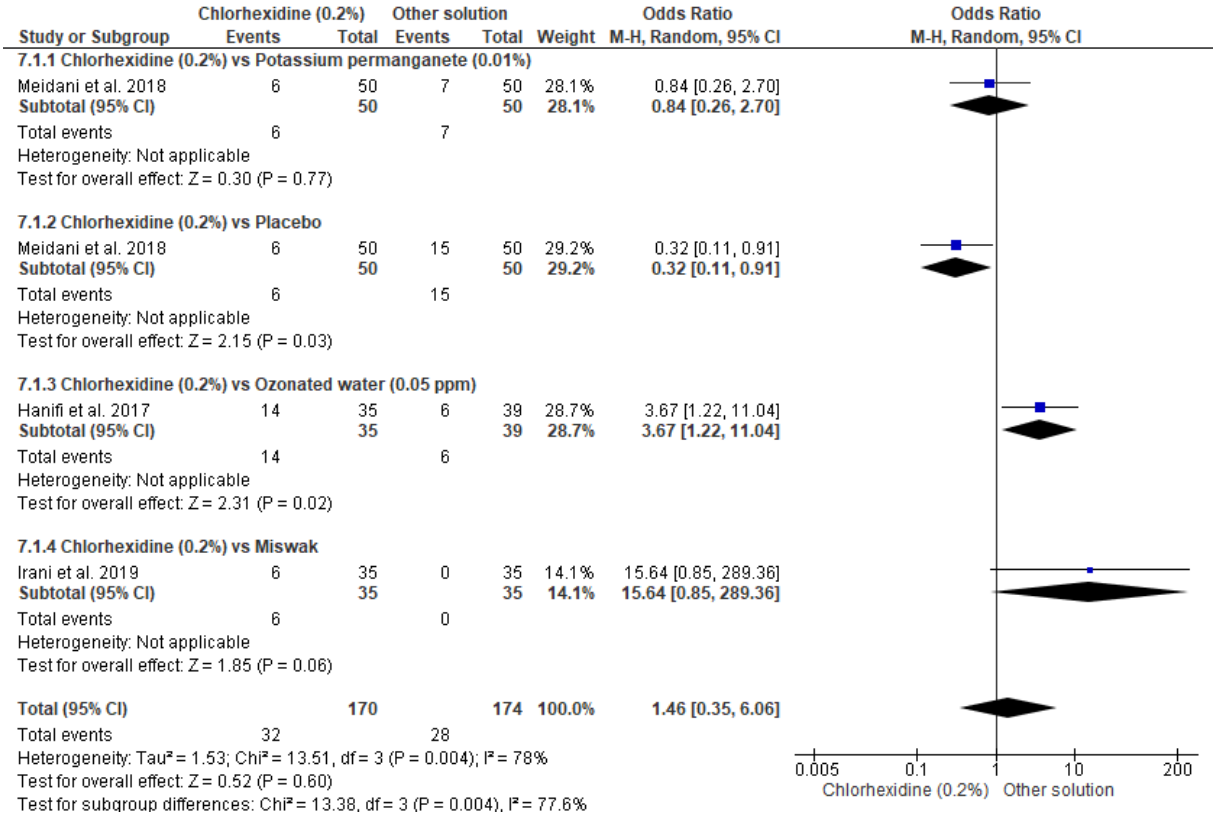
Ten studies included in this systematic review investigated the effect of oral care solutions on the development of VAP. In three of these studies, 2% chlorhexidine solution was compared with nanosil mouthwash in one study (Khaky et al., 2018, pp. 206-209), and with 0.9% NaCl (Tuon et al., 2017, pp. 159-163) and 0.2% chlorhexidine in the other study (Zand et al., 2017, pp. 318-322). According to the combined results of these studies, VAP infection was detected 1.67 times more in the 2% chlorhexidine solution group however this result was not statistically significant (OR: 1.67, 95%: 0.12 to 22.89, Z= 0.38, p= 0.70; Figure 2). However the sub-group analysis showed that the incidence of VAP infection was approximately 11 times more in the 2% chlorhexidine group than Nanosil mouthwash group and this difference was statistically significant (OR: 11.32, 95%: 1.36 to 94.25, Z= 2.24, p= 0.02). Again when 2% chlorhexidine solution was compared with 0.2% chlorhexidine solution, it was found that the incidence of VAP infection was statistically significantly lower in the 2% chlorhexidine group (OR: 0.19, 95%: 0.05 to 0.70, Z= 2.49, p= 0.01). On the other hand, when 2% chlorhexidine solution was compared with 0.9% NaCl, both groups were statistically similar (OR: 3.00, 95%: 0.36 to 24.92, Z= 1.02, p= 0.31; Figure 2).

Figure 2: Meta-Analysis Findings for 2% Chlorhexidine Solution Compared with Other Solutions



In three studies reviewed in this systematic review, 0.2% chlorhexidine solution was compared with 0.05 ppm ozonated water (Hanifi et al., 2017, pp. 1-8), miswak (Irani et al., 2019, pp. 1-7), 0.01 potassium permanganete and control group (Meidani et al., 2018, pp. 1-4). According to the combined results of these studies, the VAP infection developed 1.46 times more in the 0.2% chlorhexidine solution group, but this result was not statistically significant (OR: 1.46, 95%: 0.35 to 6.06, *Z*= 0.52, *p*= 0.60, *I2*= 78). In the sub-group analysis, it was found that the VAP infection was seen about 3.67 times higher than the 0.05 ppm ozonated water group in the 0.2% Chlorhexidine solution group and this difference was statistically significant (OR: 3.67, 95%: 1.22 to 11.04, *Z*= 2.31, *p*= 0.02). However, VAP infection was found to be statistically significantly less common in the 0.2% chlorhexidine solution group than in the control group (OR: 0.32, 95%: 0.11 to 0.91, *Z*= 2.15, *p*= 0.03). On the other hand, it was observed that the 0.2% chlorhexidine solution group was statistically similar to the potassium permanganete and miswak groups in terms of the probability of developing VAP infection (respectively OR: 0.84, 95%: 0.26 to 2.70, *Z*= 0.30, *p*= 0.77 and OR: 15.64, 95%: 0.85 to 289.36, *Z*= 1.85, *p*= 0.06; Figure 3).

Figure 3: Meta-Analysis Findings for 0.2% Chlorhexidine Solution Compared with Other Solutions



One study compared 2% chlorhexidine solution with 5% glutamine solutions (Kaya et al., 2018, pp. 10-14). Results of this study showed that the difference between groups in terms of CPIS score was not statistically significant (MD: 0.29, 95%: -0.56 to 1.14, *Z*= 0.67, *p*= 0.50).

One study compared 0.1% chlorhexidine solution with Lp299 solutions (Klarin et al., 2018, pp. 272). VAP infection was detected 1.8 times more in the 0.1% chlorhexidine solution group, however this result was not statistically significant (OR: 1.80, 95%: 0.58 to 5.63, *Z*= 1.02, *p*= 0.31).

In a study included in the systematic review, 0.12% chlorhexidine solution and placebo group (sodium bicarbonate) were compared (Kes et al., 2021, pp. 228-234). It was determined that 0.12% chlorhexidine solution reduced the possibility of developing VAP infection, but this result was not statistically significant (OR: 0.34, 95%: 0.12 to 1.00, *Z*= 1.96, *p*= 0.05).

A study included in this systematic review compared hydrogen peroxide and NaCl groups in preventing VAP infection (Nobahar et al., 2016, pp. 444-450). Findings of this study showed that VAP infection was statistically significantly lower in the hydrogen peroxide group (OR: 0.28, 95%: 0.09 to 0.90, *Z*= 2.13, *p*= 0.03).

3.5. Harmful or adverse effects of oral care solutions

Nine of the studies included in this systematic review did not report any adverse effect/unanticipated effect caused by oral solutions used in these studies. Only one of the studies reported adverse effects. In that study 2 patients reported discoloration in teeth (3.5%),

1 patient reported oral mucosa irritation (1.8%) in the 2% chlorhexidine group and 1 patient reported oral mucosa irritation (1.8%) in 0.2% chlorhexidine group (Zand et al., 2017, pp. 318-322).

4. DISCUSSION

This systematic review and meta-analysis which evaluated the effectiveness of oral care solutions in preventing VAP in patients on MV presents combined results of 10 randomized controlled trials published between 2016 and 2022. Meta-analysis findings are important since they reveal important results about development of VAP in patients on MV.

In our analysis we found that there was no statistically significant difference for VAP incidence between 2% chlorhexidine solution and nanosil mouthwash, 0.9% NaCl and 0.2% chlorhexidine. A previous randomized controlled trial reported that 2% chlorhexidine was more effective and safer compared to 0.9% NaCl in preventing VAP in patients on MV (Tantipong et. al, 2008, pp. 131-136). In their randomized controlled trial Sharma and Kaur (2012, pp.169-178) found that 0.12% chlorhexidine was significantly effective in preventing VAP compared to saline solution. In their study to determine the effect of 2% chlorhexidine in VAP incidence, Meinberg et al. (2012, pp. 369-374) found that VAP incidence in the group that received oral care with 2% chlorhexidine (64.3%) was statistically significantly higher than the placebo group (45.8%). Cabov et al. (2010, pp. 397-404) found that 0.2% chlorhexidine solution was more effective in preventing VAP compared to placebo. Another study found that development of VAP was significantly reduced in 0.12% chlorhexidine group compared to the place group (Grap et al., 2011, pp. 115-122). In a double-blind randomized controlled trial that investigated the effect of chlorhexidine in different concentrations on microbial colonization, 2%, 1%, 0.2% and 0.12% chlorhexidine were compared and 2% and 1% chlorhexidine concentrations were effective in reducing microorganisms responsible for development of VAP (Özdemir and Türk, 2022, pp. 1-9). When the studies on the subject were reviewed, although there are limited number of studies that found that 2% chlorhexidine solution is more effective than 0.9% NaCl solution to prevent VAP, there are no studies that compared 2% and 0.2% chlorhexidine, 0.9% NaCl and nanosil solutions together. Therefore our study findings are similar to the literature and the reason for this could be that there is no study that compares all of these solutions in the same study and the number of studies that met the inclusion criteria is limited.

In our analysis we found that there was no statistically significant difference for VAP incidence between 2% chlorhexidine solution and lactobacillus plantarum 299 (Lp299) solution. Although there are studies in the literature which evaluated the effect of 0.1% chlorhexidine solution as oral care in preventing VAP in patients on MV, there is no evidence for Lp299 solution. Therefore no comparison can be done to show which of these two solutions is more effective. Studies that evaluate the effect of Lp299 solution when used as oral care for patients on MV on the development of VAP are needed.

In our analysis, 2% chlorhexidine solution was compared with 5% glutamine and no statistically significant difference between these two solutions was found for development of VAP. When the literature was reviewed, glutamine was investigated mostly for its effects on mucositis in chemotherapy patients and no study which investigates its effects on VAP development was found (Choi et al., 2007, pp. 57-62; Ward et al., 2009, pp. 134-140; Cockerham et al., 2000, pp. 300-303). The studies on this subject provide evidence that 2%

chlorhexidine solution is effective on the development of VAP with or without glutamine (Özdemir and Türk, 2022, pp. 1-9; Tantipong et al., 2008, pp. 131-136). As there is only one study in the literature that evaluates the use of glutamine solution in oral care and its effects on VAP, it is not possible to come to a conclusion about which of these solutions is more effective.

In our analysis 3% hydrogen peroxide and 0.9% NaCl used as oral care solutions were compared and VAP incidence in the hydrogen peroxide group was statistically significantly lower than NaCl group. The only study in the literature, which evaluated the effect of hydrogen peroxide did not find any significant difference between 0.12 % chlorhexidine, 1.5% hydrogen peroxide and 8.4% sodium bicarbonate for preventing development of VAP (Palloş, 2018, pp.49-76). This study's findings and our study findings are not comparable. We believe that the reason for this is that a lower concentration hydrogen peroxide was used in that study and the solution was not compared with 0.9% NaCl but with other solutions.

Only one of the studies included in this meta-analysis reported discoloration on teeth and oral mucosa irritation in a few patients associated with the use of chlorhexidine solution as oral care. Limited number of adverse/unanticipated effects of the solutions was reported in the studies selected from the literature. In their study Tantipong et al. (2008, pp. 131-136) reported mild and reversible oral mucosa irritation in the chlorhexidine group (9.8%-10 patients) and in the normal saline group (0.9% - 1 patient). A previous meta-analysis study reported no adverse effect associated with oral care solutions (Chlebicki and Safdar, 2007, pp. 595-602). Types and incidence of adverse events reported in our study are similar to the adverse events reported in the literature. In order to have a comprehensive evaluation, information on any adverse/unanticipated events as a result of the use of oral care solutions needs to be reported.

In this study, it was found that 0.12% chlorhexidine solution had a similar effect with the sodium bicarbonate group in terms of the probability of developing VAP infection. In the literature, there are studies evaluating the effect of 0.12% chlorhexidine and sodium bicarbonate solution on the prevention of VAP in the oral care of patients under MV, but a study was found in which the effect was compared in the same study. In the only study in the literature; 0.12% chlorhexidine and 8.4% sodium bicarbonate solutions used in oral care were compared and it was found that there was no significant difference between them in terms of preventing the development of VAP (Palloş, 2018, pp. 49-76). Compared to this single study, 0.12% chlorhexidine and sodium bicarbonate were not superior to each other in preventing VAP, therefore it is thought that more studies are needed to evaluate the effect on VAP.

In this meta-analysis, it was determined that 0.05 ppm ozonated water was statistically significantly more effective than 0.2% chlorhexidine solution in reducing the possibility of developing VAP infection. Kshitish and Laxman (2010, pp. 341-348) reported that ozonated water caused a reduction of more than 0.2% chlorhexidine in oral microorganisms. However, although there is a lack of research in the literature on the effect of ozonated water use in oral care on the prevention of VAP infection, there is information about the application of ozonated water that reduces the number of microorganisms in the mouth and prevents the reproduction of microorganisms. Therefore, it can be said that oral care with ozonated water has a preventive effect on VAP infection compared to 0.2% chlorhexidine.

In this systematic review, it was determined that 0.2% chlorhexidine solution significantly decreased the development of VAP compared to the placebo group and had a similar effect with potassium permanganete and miswak applications. In a study conducted; It was found that there was no significant difference between 0.2% chlorhexidine and 0.01 potassium permanganate solutions used in oral care in terms of VAP prevention (Panchabhai et

al., 2009, pp.1150-1156). Our research findings are similar to this study. In the literature, there are studies evaluating the effect of 0.2% chlorhexidine solution on the prevention of VAP in the oral care of patients under mechanical ventilator support, but there is no other evidence for the use of miswak. Therefore, a comparison of which of these two solutions is more effective cannot be made. There is a need for studies evaluating the effect of miswak solution on VAP in the oral care of patients on mechanical ventilator support.

4.1. Strengths and limitations of the study

Using a comprehensive search strategy and inclusion of recent randomized controlled trials in this systematic review and meta-analysis are the strengths of this study. However lack of sufficient number of studies to be included in this review and small sample size and lack of homogeneity in comparison groups and in antiseptic solutions is the limitations of this study. To control this situation, the Random Effect model was chosen in analyses with high heterogeneity between studies. In addition, another limitation of the study is that network meta-analysis cannot be performed to determine which solution is less effective and which solution is more effective. Therefore, in the meta-analyzes performed, the results were presented by taking these limitations into consideration.

5. CONCLUSION

In this meta-analysis, it was concluded that 2% chlorhexidine solution was more effective than 0.2% chlorhexidine solution and less effective than nanosil mouthwash solution in terms of reducing the possibility of VAP infection, and had a similar effect with 0.9% NaCl and 5% glutamine. Also in this study, it was determined that 0.2% chlorhexidine solution was less effective than 0.05 ppm ozonated water in terms of reducing the possibility of VAP infection, and it was similar to potassium permanganete and miswak. In addition, in this systematic review, it was concluded that 3% hydrogen peroxide was more effective than 0.9% NaCl in reducing the possibility of VAP infection, 0.1% chlorhexidine solution and Lp299 solution, and 0.12% chlorhexidine solution and sodium bicarbonate had similar effects.

Based on these results, stronger evidence is needed to reach to a conclusion about which of the oral care solutions are more effective in preventing VAP in patients on MV. It is recommended that further randomized controlled trials that investigate especially the effect of Lp299, glutamine, ozonated water, povidone iodine and hydrogen peroxide solutions in preventing the development of VAP and report any adverse/unanticipated events of these solutions should be done.

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