Efficacy of Chlorhexidine Versus Listerine Perioperative Mouthwash in Preventing Ventilator-Acquired Pneumonia: An Integrative Review

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Abstract

**Objective:** To compare the safety and efficacy of chlorhexidine versus Listerine in perioperative and intensive care settings in preventing ventilator-acquired pneumonia (VAP). **Methods:** An integrative review using a keyword search was conducted in Cochrane, Cinahl, and Google Scholar databases. Data was collected regarding the efficacy of chlorhexidine and Listerine in preventing ventilator-acquired pneumonia, safety and side effect profiles, and *in vivo*/*in vitro* secondary outcome measures. **Results:** Chlorhexidine demonstrates superiority to Listerine in reducing ventilator-acquired pneumonia. Secondary *in vivo* tests including plaque and gingivitis reduction, and *in vitro* tests measuring the effect on bacterial loads, also favors chlorhexidine over Listerine. Chlorhexidine has shown to have significantly more side effects compared to Listerine. **Conclusions:** Chlorhexidine is justifiably used in preventing ventilator-acquired pneumonia over Listerine. There is a gap in knowledge due to the lack of randomized-controlled trials utilizing Listerine in VAP bundles. Future research should focus on finding an alternative mouthwash to chlorhexidine that is equally effective at reducing VAP incidence, but lacks chlorhexidine’s undesirable side effect profile.

**Keywords:** chlorhexidine, Listerine, ventilator-acquired pneumonia
INTRODUCTION

Ventilator-Acquired Pneumonia (VAP) is defined as pneumonia that has developed after mechanical ventilation of 48 hours or longer. Diagnosis is made when new or worsening infiltrates are detected by chest radiography (CXR) with two or more accompanying factors (Table 1). Despite recent advances in recognition and prevention, VAP continues to be a significant problem. Incidence is 9-28% of mechanically ventilated intensive-care (ICU) patients with an estimated mortality of 12%. VAP costs an additional $11 000-$49 000 per patient to treat and increases hospital length-of-stay by six to nine days.

VAP prevention has been the culmination of multiple evidence-based interventions that have shown to reduce VAP rates by as much as 64%. Collectively, these interventions are called a VAP bundle (Table 2) and include oral decontamination with 30 ml of chlorhexidine (CHX) 0.12% mouthwash, also known by the brand name Peridex. CHX is used in 60-70% of VAP bundles in the ICUs of Europe and North America and has independently shown to reduce VAP rates by as much as 30-40%.

Numerous randomized controlled trials (RCTs) of CHX have been conducted showing efficacy in VAP prevention. Nonetheless, CHX may produce unwanted side effects including supragingival calculus, tooth discoloration, and a bitter taste. Previous research advocating the use of CHX has been called into question due to limitations of the studies. Listerine, also known as Essential Oil Mouthwash (EOMW), is a popular mouthwash that has had numerous uses for over 100 years and has been extensively studied. The purpose of this integrative review is to compare CHX versus Listerine using VAP as a primary outcome measure. Secondary comparative measures include in vivo factors such as plaque and gingivitis indices, in vitro measures of bacterial inhibition, and a side-by-side comparison of safety and side effect profiles.
METHODS

Guiding questions used in this integrative review include: What are the implications of mouthwash in VAP prevention? What are the differences in safety and efficacy between CHX and Listerine? What effect does routine preoperative mouthwash have on perioperative/postoperative complications?

Initially, keyword searches were conducted in February 2017 using the terms; chlorhexidine OR Listerine AND ventilator-associated pneumonia in the Cochrane (2912 results), Cinahl (3259 results), and Google Scholar (130 results) databases. Article titles and abstracts were combed to determine relevancy. Studies pertaining to systematic reviews, perioperative mouthwash, and side effect profiles were given emphasis for inclusion. Approximately 15 articles were initially selected. In reading these articles, select references made by authors as to the side effects or secondary outcome measures were noted, and subsequently included in this review. Study data were compiled into an evidence matrix and data table. The data table was categorized by independent and dependent variables along with the results.

RESULTS/LITERATURE REVIEW

Oral Mouthwash

History and Mechanism of Action. The bactericidal effects of polydiguianides were initially discovered in the 1950s during laboratory testing of their biological properties.11 CHX is a bisbiguanide and a descendent of these early formulations. The mechanism of action results from electrostatic binding of CHX to the bacterial surface. Bacterial cell wall integrity is disrupted resulting in leakage of bacterial cellular contents and cell death.8 The antimicrobial activity of CHX is immediate and has been found to last up to seven hours after administration.1
Studies have shown that susceptible organisms include a wide variety of bacteria, viruses, and fungi.\textsuperscript{12} The only commercially available oral formulation found in the United States is CHX Gluconate 0.12\%, although human studies have also included concentrations of 0.2\%, 1\%, and 2\%.\textsuperscript{1} CHX is directed to be used as a swish-and-spit of 30 ml volume.

Listerine was created in 1879 as a mixture of essential oil compounds including menthol (mint) 0.042\%, thymol (thyme) 0.064\%, methyl salicylate (wintergreen) 0.06\%, and eucalyptol (eucalyptus) 0.092\%, dissolved in 26.9\% alcohol. Named after the father of modern antisepsis, Joseph Lister, Listerine was originally marketed as floor cleaner, dandruff reducer, and breath freshener. It was not until the 1970s that the plaque and gingivitis preventative properties were discovered.\textsuperscript{13} Listerine exhibits antimicrobial properties via perforation of the bacterial cell membrane causing content leakage and death. It produces anti-inflammatory properties by inhibiting prostaglandin formation and by altering neutrophil function through scavenging of free radicals. Listerine has shown efficacy against a wide range of bacteria, viruses, and fungi; although neither Listerine nor CHX is approved for the prevention or treatment of viral infections.\textsuperscript{8}

**Safety and Efficacy.** Guidelines for oral mouthwashes and their use in gingivitis and plaque prevention have been established by the American Dental Association (ADA) and the Food and Drug Administration (FDA) starting in the 1980’s. The ADA awards the Seal of Acceptance to mouthwash products that are tested in RCTs, parallel-group trials or crossover clinical trials with a control or comparison group. The product must have at least two trials lasting six months or longer with an intermediate evaluation at three months. Studies must show a statistically significant reduction in gingivitis and plaque as well as establish safety with respect to soft tissues, teeth, toxicology, and effects on oral flora. The ADA seal of acceptance
has only been awarded to Listerine and CHX 0.12% for control of supragingival plaque and gingivitis. Due to changes in the ADA seal program, CHX no longer carries the ADA seal.8

The FDA regulates prescription and over-the-counter (OTC) drugs within the United States. The Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Panel was established in 2003 by the FDA. This committee examined mouthwash products for safety and efficacy through a process which evaluated adverse reactions, margin of safety, potential for abuse, and risk-benefit ratio. Listerine was deemed safe and effective by the FDA. CHX was approved as safe and effective by a lengthier process called the New Drug Application, and is available in the United States by prescription only.8

**Side Effects.** The ADA and FDA have deemed CHX and Listerine safe. Any discussion regarding side effects must consider that reactions are mild and temporary without resulting in long-term sequelae. Based on a systematic review of 19 studies (n=826), Neely14 summarized that CHX is associated with more tooth staining than Listerine. Haydari et al15 concluded from a RCT (n=40) that over 70% of CHX subjects had tooth discoloration. Furthermore, over 50% of users complained of CHX being too bitter, tasting bad, or making them nauseated. CHX produced temporary symptoms such as loss of taste in 55%, numb feeling on the tongue in 20%, soreness in 35%, and a dry mouth in 25% of participants. Similarly, Supranato et al9 found that 30% of CHX users described the tooth discoloration as unacceptable (n=157). Conversely, Spreadborough et al5 claimed that only 1 in 500 patients complained of tooth discoloration while using CHX 0.2%.

Quantifiable data on the adverse effects of Listerine was scarce. Beyond a burning sensation during use, few side effects are found in the literature. Al Habashneh et al16 showed no
significant increase in Calculus Index (CI) or Staining Index (SI) compared to control, whereas CHX demonstrated a statistically significant increase in both indices.

**VAP as the Primary Outcome Measure**

**Chlorhexidine and VAP.** CHX has been found to reduce VAP in various populations. Hua et al\(^1\) conducted a systematic review of 18 RCTs (n=2451) involving ICU patients who were mechanically ventilated greater than 48 hours. CHX significantly reduced VAP incidence from 25% to 19% (RR=0.74, 95% CI=0.61-0.89, I\(^2\)=64%, p=0.02). Major cardiac surgical patients were studied by Spreadborough et al\(^5\) in a systematic review of four RCTs (n=2205). CHX significantly reduced VAP in this population from 10.3% to 5.3% (RR=0.52, 95% CI=0.39-0.71, I\(^2\)=0%, p<0.01). Klompas et al\(^7\) conducted a systematic review of 13 RCTs (n=905) evaluating noncardiac surgical patients. The VAP rate of 17% in the CHX group was not a significant reduction from the control VAP rate of 20% (RR=0.78, 95% CI=0.60-1.02, I\(^2\)=44%, p=0.36).

The effect of concentration and frequency of CHX use on VAP rates were explored by Villar et al\(^1\) in a systematic review of 13 RCTs (n=1634). Using intention-to-treat, and sub-group analyses, Villar et al\(^1\) revealed that CHX concentration of 2% and a frequency of four times per day (QID) significantly reduced VAP. Concentrations of 0.12%, 0.2%, and frequencies of once per day (QD), twice per day (BID), and three times per day (TID) did not significantly reduce VAP.

**Listerine and VAP.** There is a relative paucity of data in the literature regarding Listerine and VAP prevention. Berry\(^10\) conducted a single-blind RCT (n=265) in patients intubated greater than 96 hours. The difference in Listerine group VAP rate of 4.3% was not statistically significant from the control VAP rate of 4.7% (RR=0.99, 95% CI=0.31-3.16,
p=0.92). Houston et al\textsuperscript{18} compared Listerine to a CHX control group in a RCT (n=561) of cardiac surgical patients without controlling for length of intubation while using an intention-to-treat analysis. More than 86\% of the participants included in the analysis were extubated in less than 24 hours. Houston et al\textsuperscript{18} found that the CHX VAP rate of 1.5\% was not statistically different than the VAP rate of 3\% in the Listerine group (p=0.21). Further analysis reveals that the VAP rate of patients who were intubated greater than 24 hours increased to 24.3\% (9 out of 37 patients) in the Listerine group while increasing to just 10.3\% in the CHX group (4 out of 37 patients).

**Routine Preoperative Mouthwash and VAP.** Although the exact mechanism of VAP is unclear, one theory posits that passing the ETT through the microbial rich oropharynx during intubation results in contamination of the ETT tip and advancement of bacteria deeper into the lungs.\textsuperscript{19} It could be extrapolated that a single preintubating dose of mouthwash would disinfect the oropharynx and decrease the risk of VAP. The efficacy of preintubation dosing of mouthwash has been explored by several authors.

Nicolosi et al\textsuperscript{20} conducted a quasi-experimental study (n=300) comparing VAP rates in patients who received CHX 0.12\% BID for three days prior to elective cardiac surgery to a historical control group. Patients in the historical control group had cardiac surgery three years prior, and did not receive a preoperative dose of CHX. The VAP rate in the CHX group was 2.7\% compared to 8.7\% in the historical control group (p=0.04). Lin et al\textsuperscript{21} also conducted a single-blind RCT (n=94) of cardiac surgical patients. The intervention group received CHX QID on the day prior to surgery while the control group did not. Both groups received similar VAP prophylaxis postoperatively including CHX QID while mechanically ventilated. Clinical Pulmonary Infection Scoring (CPIS) is an objective numeric scoring system often used as a
surrogate diagnostic tool in identifying VAP. Higher CPIS scores indicate increased probability of pulmonary infection. CPIS scores were recorded on postoperative days (POD) 1, POD 3, and POD 5 in all patients who remained intubated. CPIS scores were not significantly different on POD 1, but the CHX group demonstrated significantly lower VAP rates (as defined as CPIS scores greater than or equal to six) than the control group on PODs 3, and 5.

Munro et al\textsuperscript{19} conducted a RCT (n=314) of surgical patients as well as patients requiring urgent/emergent intubations outside of the operating room. The intervention group received a single dose of CHX 0.12\% immediately prior to intubation, while the control group was intubated without CHX. Both groups received CHX BID and similar prophylactic measures post-intubation. CPIS scores were collected from POD 0 to POD 6 following intubation on all patients who were not yet extubated. Furthermore, the endotracheal tube (ETT) tip was cultured upon extubation in 83 participants and evaluated for bacterial colonization. Findings demonstrated no significant difference in CPIS scores (less than six in both groups) and colonization rates (less than 20\% in both groups).

**Secondary Outcomes**

**Plaque and Gingivitis.** *In vivo* outcome measures of mouthwash efficacy include plaque and gingivitis reduction. Vlachojannis et al\textsuperscript{22} performed a systematic review of 16 studies (n=2122) on the effects of CHX versus Listerine on Plaque Index (PI) scores. Both mouthwashes significantly reduce plaque compared to control, but CHX reduced PI scores significantly more than Listerine. DePaola and Spolarich\textsuperscript{8} found similar results in a systematic review of 9 RCTs (n=2176) CHX reduced PI by 42\% on average versus 35\% for Listerine. Neely’s\textsuperscript{14} systematic review of 7 studies (n=826) concluded that CHX reduced PI scores significantly more than Listerine in 5 of 7 studies.
DePaola and Spolarich\textsuperscript{8} conducted a systematic review of 9 studies (n=2176) comparing effects of CHX versus Listerine on gingivitis. Both agents significantly reduced gingivitis compared to control, with CHX reducing gingivitis by 35\% on average compared to 21\% for Listerine. Vlachojannis et al\textsuperscript{22} and Neely\textsuperscript{14} performed systematic reviews revealing similar results. CHX equaled or outperformed Listerine in reducing gingivitis, while both reduced gingivitis significantly greater than control.

**Bacterial Counts.** The bactericidal effects of mouthwash are measured \textit{in vitro} using microbial counts, total bacterial counts, Colony Forming Units (CFUs), Zone of Inhibition (ZOI), or bacterial vitality tests. Agarwal\textsuperscript{23} compared CHX to Listerine on CFUs (n=45) finding that CHX reduced CFUs by 52\% versus 45\% in Listerine. Haerian-Ardakani et al\textsuperscript{24} found that CHX reduced CFUs by 86\% compared to 71\% in Listerine (n=32). Gultz\textsuperscript{25} found that CHX reduced microbial counts by 49\% compared to 37\% in Listerine (n=20).

Haerian-Ardakani et al\textsuperscript{24} studied the effects of mouthwash on ZOI. CHX significantly reduced the ZOI by 18.38 mm while Listerine did not have any effect on ZOI compared to control (n=32). Zheng and Wang\textsuperscript{26} found that CHX significantly reduced total bacteria counts from 6.6 million to 5.3 million CFUS/ml (p<0.05) while Listerine did not significantly reduce total bacteria counts from 6.67 million to 6.60 million in the control group (n=18). Lastly, Quintas et al\textsuperscript{27} found that both CHX and Listerine significantly reduced bacterial vitality, but Listerine had a greater impact on bacterial vitality than CHX for a longer period. CHX reduced bacterial vitality from 73\% to 5\% immediately after use, climbing steadily to 33\% after seven hours. Listerine reduced bacterial vitality from 73\% to 1\% immediately after use, climbing steadily to only 17\% after seven hours (n=15).
Mortality, Duration of Ventilation, and ICU Length of Stay. Although the negative effects of VAP on hospital cost, mortality, and hospital length-of-stay are well documented, mouthwash as an independent factor has not shown to reduce mortality, duration of ventilation or ICU length-of-stay. This has been confirmed by many authors and in multiple systematic reviews and clinical trials. 5, 7, 13, 17, 28

DISCUSSION

VAP continues to be the most commonly utilized outcome measure of mouthwash efficacy. This is despite claims by Klompas et al7 that duration-of-ventilation, length-of-stay and mortality would be less biased means to measure effectors of pneumonia in the intubated patient. Dozens of RCTs and multiple systematic reviews of CHX in numerous clinical settings indicates that CHX significantly reduces incidence of VAP.5,17 The two RCTs involving Listerine are neither conclusive nor current, and provide little strength in arguing for the widespread use of Listerine for VAP prevention.10,18

Adding a preoperative dose of CHX to the existing VAP bundle has been shown to decrease rates of VAP in specific surgical populations.20,21 Research by Nicolosi et al20 and Lin et al21 demonstrated that patients undergoing major cardiac surgical operations, who are expected to be intubated longer than the average surgical patient, have shown protection from VAP when a preoperative dose or regimen of CHX is administered. This may prompt the question of whether routine preoperative mouthwash could have potential benefits in all surgical populations and settings. Munro et al19 refutes this assertion in their findings, demonstrating that patients intubated in broad settings and populations do not benefit from a single dose of CHX before intubation. Studies utilizing multiple doses of mouthwash prior to non-cardiac surgery were
unable to be found in the literature, leaving it unclear what effect this more stringent preoperative dosing regimen would have on VAP in this broad population.

The ADA and the FDA have rigorously evaluated the overall safety of CHX and Listerine along with their efficacy in preventing plaque and gingivitis. Both, having been deemed safe and effective, makes secondary characteristics such as side effect profiles important in choosing superiority. Although not particularly dangerous nor permanent, side effects of CHX including calculus formation, tooth discoloration, and taste/sensation disturbances may make Listerine a more attractive choice of mouthwash, especially in the conscious unintubated patient.

Using a side-by-side comparison between CHX and Listerine, it is evident that both agents significantly reduce plaque, gingivitis, CFUs, microbial counts, and bacterial vitality. CHX appears to have an advantage over Listerine in decreasing plaque, gingivitis, CFUs, microbial counts, total bacterial counts, and ZOI tests. Listerine does not appear to influence ZOI and total bacterial counts. Listerine has shown to decrease bacterial vitality more effectively than CHX. Without consensus in the literature about the reliability and validity of the stated in vitro tests, nor their aptitude in predicting VAP, determining a clear winner is difficult. CHX is on par, or superior to Listerine in all categories except bacterial vitality, and presents a strong argument as a better bactericidal agent.

**Strength/Weaknesses of this Integrative Review**

Special attention was paid in including systematic reviews and RCTs within the integrative review to add validity to the findings. There was ease in finding sufficient data on CHX, but some difficulty in identifying high level evidence for Listerine. Having few trials to compare VAP between mouthwashes, secondary outcomes were needed as an alternative
comparison between CHX and Listerine. These secondary outcomes show no definitive
correlation with VAP, and using them as a tool for comparison can be argued as invalid.
Furthermore, the literature review is intended as a broad assessment of multiple end points to
give a wide range of perspectives on the comparison between CHX and Listerine. In no way is
the literature review exhaustive or meant to encompass all available research on this topic.

**Recommendations for Practice**

Without definitive evidence demonstrating the parity of Listerine with CHX in
preventing VAP, the current practice of using CHX within VAP bundles is appropriate. There is
not currently sufficient evidence to recommend routine preoperative CHX in all populations and
settings; but major cardiac surgical patients should continue to receive a preoperative dose of
oral CHX swish-and-spit prior to their procedure.

Although the most popular concentration of CHX is 0.12% with a frequency of BID,
current evidence suggests that the ideal dose of CHX is 2% with a frequency of QID. This is
based on two and three RCTs, respectively. Due to the limited number of trials at this higher
dose and frequency, more research should be conducted to determine whether this change is
necessitated, and if so, how the prevalence of adverse events will be affected.

Listerine use results in fewer side effects compared to CHX, and evidence of VAP
prevention would make the choice of Listerine over CHX clear. Future research should focus on
exploring the use of Listerine in VAP bundles and in the preoperative setting. CHX remains the
standard of care for perioperative mouthwash and any trials should include a CHX comparison
group along with the standard placebo control group.

The use of VAP as an objective measure of lung dysfunction in the ventilated patient has
been called into question. Klompas argues that using VAP as a diagnostic tool is notoriously
subjective, inaccurate and lacking in sensitivity and specificity. Audits conducted by Nussenblatt et al\textsuperscript{30} reveal that as many as 75% of patients treated for VAP did not likely have pneumonia. Ventilator-Associated Event (VAE) is a more current and broader measure of ventilator-acquired lung disease, and is becoming more popular. Future research should incorporate VAE in addition to, or in lieu of, outdated measures like CPIS and VAP in determining prevalence of pulmonary infection.

CONCLUSIONS

VAP continues to be a costly problem in the ICU. Current VAP bundles are useful in reducing VAP rates and current evidence supports the inclusion of CHX 2% mouthwash QID in all mechanically ventilated patients. Patients preparing for major cardiac surgery should receive a dose of CHX within 24 hours prior to their procedure. Although useful for reducing plaque and gingivitis, Listerine has insufficient supporting evidence to supplant CHX in VAP bundles or preoperative dosing. In a side-by-side comparison (Table 3), CHX demonstrates to be advantageous to Listerine over multiple end-points. Due to the unwanted side effects of CHX, more research is warranted in finding a suitable alternative. Listerine has a more favorable side effect profile compared to CHX, as well as promising \textit{in vivo} and \textit{in vitro} studies to warrant increased trialing.
References


### Table 1: Criteria for VAP

New or Worsening Infiltrates on CXR AND Two or More of the Following:

- Temperature $> 38.5\,^\circ C$ or $< 35.0\,^\circ C$
- WBC $> 11,000/mm^3$ or $< 4,000/mm^3$
- Purulent secretions from lungs/airway
- Positive tracheal or bronchoalveolar lavage cultures
- Increase in FiO$_2$ or PEEP by more than 20% to keep SpO$_2 > 92\%$
Table 2: VAP Bundle Interventions

- Head-of-Bed (HOB) elevation > 30°
- Deep Vein Thrombosis (DVT) prophylaxis
- Peptic Ulcer Disease (PUD) prophylaxis
- Endotracheal cuff pressures at 20-30 cmH₂O
- Daily sedation vacations
- Sub-glottic suctioning
- Oral decontamination with CHX every eight hours
Table 3: Summary Comparison of CHX Versus Listerine

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