

The Efficacy of Povidone-Iodine Oral Rinse in Preventing Ventilator-Associated Pneumonia: A Randomized, Double-blind, Placebo-controlled (VAPOR) Trial: Preliminary Report

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ABSTRACT

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection among mechanically ventilated patients. One of the routes for the development of VAP is aspiration of bacteria from dental plaque. It is hypothesized that reducing the oropharyngeal bacterial load would also decrease the incidence of VAP.

A randomized, double-blind, placebo-controlled trial with intention-to-treat analysis was done to determine the efficacy of povidone-iodine rinse compared to placebo in (1) preventing VAP among mechanically-ventilated intubated ICU patients; (2) lowering mortality rate; and (3) shortening duration of intubation, ICU stay and hospital stay.

The study was conducted from September 2003 to August 2004. Mechanically ventilated adult patients at the five ICUs of PGH seen within 24 hours of intubation were included in the trial. Patients with concomitant nosocomial pneumonia, confirmed hyperthyroidism, or known hyper-sensitivity to povidone-iodine were excluded.

There were two treatment arms: Group A received placebo and Group B received 1% povidone-iodine (PVP-I) oral rinse. Both were given as buccal swab every 8 hours by the ICU nurses.

The primary outcome was the incidence of VAP. Secondary outcomes included duration of mechanical ventilation, duration of ICU stay and hospital stay, and all-cause mortality rate. Adverse drug reaction to povidone-iodine was also noted. Both incidence rates of VAP and all-cause mortality were compared using risk ratios with 95% confidence intervals. A Kaplan-Meier survival curve was plotted. T-test was used to test for significant differences in the average length of ICU stay, hospital stay and intubation. A probability value < 0.05 was considered statistically significant. All reported p values were two-sided.

Forty-two patients were recruited in the study. There was a trend towards a decrease in the incidence of VAP in the PVP-I group. Kaplan-Meier analysis showed no statistically significant difference between the placebo group and the treatment group. The mean duration of intubation was 168 hours (95% CI:0.17-264 hours) for the PVP-I group and 160 hours (95% CI:12-312 hours) for the placebo group. The average ICU stay was 7.6 days (95% CI (1-24 days) for the PVP-I group and 8 days (95% CI: 1-26 days) for the placebo group. There's no statistically significant difference in the duration of intubation and ICU stay between the treatment and control groups. Mortality rates for both treatment and control groups were comparable. No adverse events directly attributable to PVP-I were noted.

The use of povidone-iodine oral rinse as prophylaxis against VAP showed a trend, albeit not statistically significant, towards benefit. It has no significant effect on lowering mortality rate and shortening length of intubation, ICU stay, and hospitalization.

Povidone-iodine oral prophylaxis is generally well tolerated. [*Phil J Microbiol Infect Dis 2004; 33(4):153-161*]

Key Words: povidone-iodine, prophylaxis, ventilator-associated pneumonia, VAP

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in mechanically ventilated patients. A study done by Berba et al in 1999 showed that the

incidence of nosocomial pneumonia among patients in the different intensive care units (ICU) of the Philippine General Hospital (PGH) was 28%. The incidence was as high as 49% among intubated patients.¹ VAP remains the leading cause of death among the hospital-acquired infections. Several studies have suggested that the mortality attributable to VAP is about 10%.^{2,3,4,5} Moreover, it extends ICU stay by as much as threefold. In the United States, the average additional cost for nosocomial pneumonia was estimated to be as high as \$1,255 per patient in 1982, \$2,863 in 1985, and the cost may even escalate to as much as \$40,000 per patient.⁶ Locally, a 7-day treatment for nosocomial pneumonia will entail an additional P8,554 to P56,070 for antibiotics alone.

Several factors are implicated in the pathogenesis of VAP. One of the routes for the development of VAP is through aspiration of bacteria from dental plaques, leading to microbial colonization of the intestinal tract. As a response to the challenge of preventing VAP and its concurrent morbidity, mortality, and increased health care costs, recent trials have focused on selective decontamination of the digestive tract. Several studies have been conducted on oral decontamination using a heterogeneous array of agents. It is presumed that by reducing oropharyngeal bacterial load, the incidence of VAP would be significantly reduced.

A survey was conducted on the practices of the nurses in the oral care of intubated patients in the central, medical, neurological, and neurosurgical ICUs of PGH (SICU not included due to technical difficulties). Ninety-one percent of the nurses said that oral rinsing with antiseptics was part of their standard oral care in intubated patients. Many of the nurses, however, were not aware of the clinical significance of the practice. The popular agents used were Bactidol (53%), povidone-iodine (22%), and potassium permanganate (1%). Most of the resident physicians did not specifically order for oral rinsing of the oral cavity as part of their patient management.

The objectives of the study are:

1. To determine the efficacy of povidone-iodine oral rinse in reducing the incidence of VAP among adult mechanically ventilated patients admitted to the intensive care unit (ICU) of the Philippine General Hospital;
2. To determine whether povidone-iodine oral rinsing in mechanically ventilated patients will decrease the mortality rate, duration of intubation, duration of hospital or ICU stay; and
3. To identify any adverse event associated with the use of povidone-iodine oral rinse.

Review of Literature

Several agents for the purpose of oral decontamination in critically ill patients have been studied. Most commonly studied disinfectants include antibiotic-based oral rinse, chlorhexidine, povidone-iodine and cetylpyridium chloriae gargle (Listerine). Different studies show that the use of oral rinse may reduce the incidence of nosocomial pneumonia but not the mortality rate and length of ICU stay.

A randomized, double-blind, placebo-controlled trial by Bergmans et al,⁷ in 2001 involving 226 mechanically ventilated patients showed a decrease in the incidence of VAP in patients who were given gentamicin/colistin/vancomycin 2% in Orabase as oropharyngeal swab. Topical prophylaxis eradicated colonization in 75% of the study

population compared to 0-9% in the control group. The incidence of VAP in the treated patients was only 10% compared to 27% for the control group. However, there was neither a difference in the length of hospital stay nor the mortality rate between the two groups. A study done by Genuit et al⁸ in 2001 involving 95 intubated patients in the surgical ICU showed that the addition of 0.12% chlorhexidine gluconate oral rinse in the weaning protocol led to a 37% overall reduction and delay in the occurrence of VAP. However, there was no significant difference in the duration of mechanical ventilation and overall hospital stay or ICU stay between the groups. Houston et al⁹ in 2002 compared the effectiveness of Listerine and chlorhexidine oral rinse as prophylaxis against nosocomial pneumonia in 561 patients undergoing cardiac surgery. They demonstrated that chlorhexidine led to a 57% overall reduction in the incidence of VAP compared to Listerine oral rinse. In patients at highest risk for pneumonia, the rate was 71% lower. The difference, however, was only statistically significant in patients intubated for more than 24 hours and who had the highest degree of bacterial colonization. In contrast to the other studies, a prospective, randomized, double-blind, placebo-controlled study by De Riso et al¹⁰ in 1996 involving 353 patients undergoing cardiac surgery showed a reduction in mortality (1.16% vs. 5.56% in the control arm) in the patients given chlorhexidine oral rinse.

Povidone-iodine (PVP-I) is a disinfectant that shows promise as an oral prophylaxis against VAP. It is an inexpensive and widely available disinfectant in paint, wash, and gargle preparations. A small study by Shiraishi and Nakagawa¹¹ in 2002 compared the bactericidal activity and patient acceptability of povidone-iodine, chlorhexidine gluconate, and cetylpyridium chloride (Listerine) gargles. The study showed that povidone-iodine had the highest reduction in oral bacterial count (99.4% vs. 59.7% for chlorhexidine and 97% for cetylpyridium). It also ranked highest in terms of taste, feeling after gargling, and odor. In this study, all test strains were killed after 30 seconds of exposure to povidone-iodine.

Summers et al¹² (2000) assessed the efficacy of preoperative decontamination of the oral cavity with povidone-iodine in a prospective randomized study involving 30 patients. A significant and sustained reduction of both oral anaerobic and aerobic bacteria was noted with povidone-iodine but not with saline. Furthermore, they claimed that the patient's age, use of preoperative intravenous cephalosporin, type-and-length of procedure did not influence the postoperative bacterial counts. In this study no patient developed an infection. A retrospective study of nosocomial pneumonia in geriatric patients done by Masaki et al¹³ in 2001, demonstrated that cleaning the upper airways with povidone-iodine as part of a stringent infection control program significantly diminished the rates of nosocomial pneumonia.

MATERIALS AND METHODS

The study was conducted at the five ICUs of the Philippine General Hospital: medical, surgical, neurological, neurosurgical, and central ICUs. Recruitment period was from September 2003 to August 2004.

Study population

Mechanically-ventilated intubated adult (age ≥ 19 years) patients admitted at the ICU and who were seen within 24 hours of intubation, were included in the investigation. Concomitant nosocomial pneumonia, whether suspected or confirmed, was a reason for exclusion. Patients with confirmed hyperthyroidism and hypersensitivity to povidone-iodine were also excluded from the study. Randomized patients who were transferred out to the ward but still intubated and mechanically ventilated were kept as study participants.

Study procedures

This was a prospective, randomized, double-blind, placebo controlled trial. Eligible patients were randomized by the use of a computer into two treatment arms: Group A received placebo (similar scent, consistency and color as that of povidone-iodine) in the form of sterile water given as a buccal swab every 8 hours; Group B received 1 % povidone-iodine (PVP-I) given as a buccal swab every 8 hours.

Nurses on duty at the respective ICUs were briefed on the proper administration of the oral rinse. Oral rinsing with either PVP-I or the placebo, was done by the ICU nurse in charge of the randomized patient.

The procedure was as follows:

1. Any particulate matter from the oropharyngeal area was rinsed off with cotton pledgets soaked in approximately 15-20 cc of sterile water.
2. Cotton pledgets were soaked in 10 cc of oral rinse solution (treatment or placebo).
3. The soaked cotton pledgets were used to swab the entire oropharyngeal mucosa and part of the endotracheal tube inside the oropharyngeal area.
4. Steps 1 to 3 were repeated every 8 hours till the end of the trial.

All patients received standard oropharyngeal care (i.e., rinsing the mouth with water, and, if possible, tooth cleaning once daily), daily chest physiotherapy, and endotracheal suctioning as needed. All patients had a nasogastric tube and gastric feeding was resumed as early as possible. Patients were given sucralfate 1 gm every 6 hours as gastric stress ulcer prophylaxis (unless previously started on a proton pump inhibitor or H₂ blocker) until feeding was resumed. Standard infection control procedures were enforced.

The caregiver, the patient, and the investigators of the primary and secondary outcomes were blinded as to the treatment arm to which the patient was assigned. Treatment and placebo oral solutions were provided by Pascual Laboratories. All preparations were delivered to the UP-PGH Central Block Pharmacy one week prior to the start of the trial for quality control testing. An independent statistician was in charge of the computer generation of the random numbers for treatment allocation. Aside from the statistician, the generated random order of allocation was made known only to the hospital pharmacists handling the distribution of either preparation. Once a patient was randomized, the investigators procured the oral rinse solution from the UP-PGH Central Block pharmacist. Only the patient's ID number was known to the investigators, ICU staff, or the patient.

Patients were followed up daily from the time of recruitment. The intervention was continued until any of the following outcomes were reached: (1) development of VAP; (2) extubation lasting more than 72 hours without development of nosocomial pneumonia; or (3) demise of the patient. Approximately 95% of the first episodes of VAP occur within the first 3 weeks of ventilation^{17,18}, thus oral prophylaxis was continued until 21 days in the absence of any of the aforementioned outcomes.

At least two of the investigators should have agreed on the diagnosis of nosocomial pneumonia. Disagreements were discussed until a consensus was reached among the three investigators. If a consensus was not possible, the research adviser was called upon to make the final decision. Incidence rates were calculated only for the first episode of nosocomial pneumonia per ICU admission.

Outcome

The primary outcome measured was the incidence of VAP as defined by U.S.. Center for Disease Control. Secondary outcomes of interest included duration of mechanical ventilation, duration of ICU and hospital stay, and all-cause mortality rate. Demographic characteristics such as age, sex, smoking and alcohol history, primary diagnosis and co-morbidities were recorded. Acute Physiologic and Chronic Health Evaluation (APACHE) II scores, Glasgow Coma Score (GCS), use of steroids, use of antibiotics, stress ulcer prophylaxis, and parameters of infection were monitored.

Data analysis

Based on the study of Berba et al, which reported a 49% incidence of hospital acquired pneumonia in critically-ill intubated patients in the Philippine General Hospital,¹ and the Bergmans study, which showed that oral decontamination decreased the incidence of VAP to about 20%,² at least 102 patients in each treatment arm was the ideal target population. With an alpha level at 0.05, the power of the study to detect a difference between treatment groups was set at 80 percent.

Intention-to-treat analysis was done. Nominal data were described and expressed as percentage. Continuous data were expressed as means with standard deviations. Both incidence rates of VAP and all cause mortality were compared using risk ratios with 95% confidence intervals. The T-test or Wilcoxon-Mann-Whitney test was used to test for statistical significance of the means of duration of ICU stay and intubation. For each patient the time until event and death was determined; the probability of survival and remaining without VAP was calculated using the Kaplan-Meier curve. Groups were compared by the log rank test. A probability value < 0.05 was considered statistically significant. All reported p values were two-sided.

Ethical considerations

The study was approved by the Research Implementation and Development Office (the institutional review board). Informed consent was obtained by the primary investigators either from the patient or, if this was not possible, from a representative of the patient (in the following order: spouse, offspring of legal age, parents, and siblings).

A written copy of the consent form (in English or in Filipino) was given to the patient or his/her representative for perusal. The terms and conditions of the consent form were explained by the investigators prior to obtaining the consent. The patient or his/her relative had the option to withdraw at any time during the trial period. Involvement in the trial did not entail additional cost to the patient or his/her family. No monetary incentives were provided. Close monitoring for any adverse reaction was done.

RESULTS

Demographic profile of the study population

Forty-two patients admitted to the different ICUs in PGH were included during the 12-month recruitment period. Reasons for exclusion were: (1) no consent obtained within 24 hours of intubation; (2) no mechanical ventilator available; (3) admitting diagnosis included hospital acquired pneumonia; (4) patient died within 24 hours of admission. Majority of the patients (n=24, 57%) were admitted at the medical ICU. The mean age of the patients upon inclusion was 53 years old (range 20 - 83 years old, SD = 16.22). There were more female (n = 25, 59.5%) than male (n=17, 40.5%) subjects. Majority of the patients came from and were intubated at the emergency room (n=25, 59.5%; n=27, 64.3%, respectively). The most commonly used ventilator was the Bennet's MA-2 (n=27, 64.3%). Acute respiratory failure (n=19, 45.2%) and decreased sensorium (n= 10, 23.8%) were the most common indications for intubation. Cardiovascular disease (n=32, 76.2%), particularly hypertension (n= 15/32,46.7%), and infectious disease (n=19, 45.2%), specifically sepsis (n=9/19, 47.4%) were the predominant co-morbid conditions. The mean APACHE II score was 17, (range 3 - 31, SD 7.52). The mean GCS score on admission and upon randomization were similar at 11 (range 3 - 15, SD=4.17 and 4.01 respectively). Majority of the patients had no alcoholic intake, while the mean pack years of smoking was 18 (range 1- 80, SD = 19.59). Sucralfate was the popular agent for stress ulcer prophylaxis (n=19, 45.2%). There was no steroid use in 34 patients (81.0%), while only 7 patients (16.7%) had no antibiotics on board.

Cephalosporins (n=19, 45.2%), in particular ceftazidime (n= 11, 26.2%), and the macrolide azithromycin (n= 14,33.3%) were the most commonly prescribed.

Out of the 42 patients randomized, 20 received placebo while 22 received PVP-I oral wash. The demographic profile of the study population showed no significant statistical differences between the treatment and the placebo groups (Table 1). All patients were followed up from the time of inclusion until a trial endpoint was reached. On the average, the PVP-I and placebo oral washes were given 11 (range 1- 35, SD= 10.84) and 10 (range 1 - 42, SD = 10.61) times, respectively, during the study period.

Primary outcomes

Fourteen (33.3%) out of the 42 patients enrolled developed VAP. Eight (40%) of the 20 patients who received the placebo developed VAP, while six (27.3%) of the 22 patients randomized to the treatment group developed VAP (Table 2). Although there is a trend towards a decrease in the incidence of VAP in the povidone-iodine group after day 7 of intubation, Kaplan-Meier analysis showed no statistical significant difference

between the two groups (Figure 1). The most common isolate for the VAP in both the PVP-I group and placebo group was *Pseudomonas aeruginosa*, followed by *Klebsiella pneumoniae*.

Table 1
Baseline demographic data

Demographics	Treatment (n=22)	Control (n=20)	p-value
Age (Mean, standard deviation)	51.4, 15.8	55.2, 16.5	0.46
Sex (males)	7 (31.8%)	10 (50.0%)	0.35
Pulmonary involvement (i.e. COPD)	7 (31.8%)	7 (35.0%)	1.00
Use of antibiotics	20 (90.9%)	15 (75.0%)	0.23
Use of steroid use	3 (13.6%)	5 (25.0%)	0.44
Sucralfate as GI prophylaxis	8 (36.4%)	11 (55.0%)	0.35
APACHE II Score (Mean, standard deviation)	15.9, 7.4	17.0, 6.7	0.62
GCS on Admission (Mean, standard deviation)	11.41, 4.51	11.25, 3.88	0.90
GCS on Randomization (Mean, standard deviation)	11.41, 4.51	11.5, 3.63	0.94
ICU Medical	12	12	
Neurologic	5	2	
Surgical	3	2	
Neurosurgical	1	1	
Central	1	3	

Table 2
Incidence of VAP and all-cause mortality

Outcomes	Treatment n=22	Control n=20	Rt	Re	RRR	ARR	95% Confidence Interval, ARR	p-value
VAP	6	8	0.27	0.40	0.32	0.13	-0.62 - 0.71	0.58
Mortality	12	10	0.54	0.50	-0.09	-0.04	-0.26 - 0.35	0.99

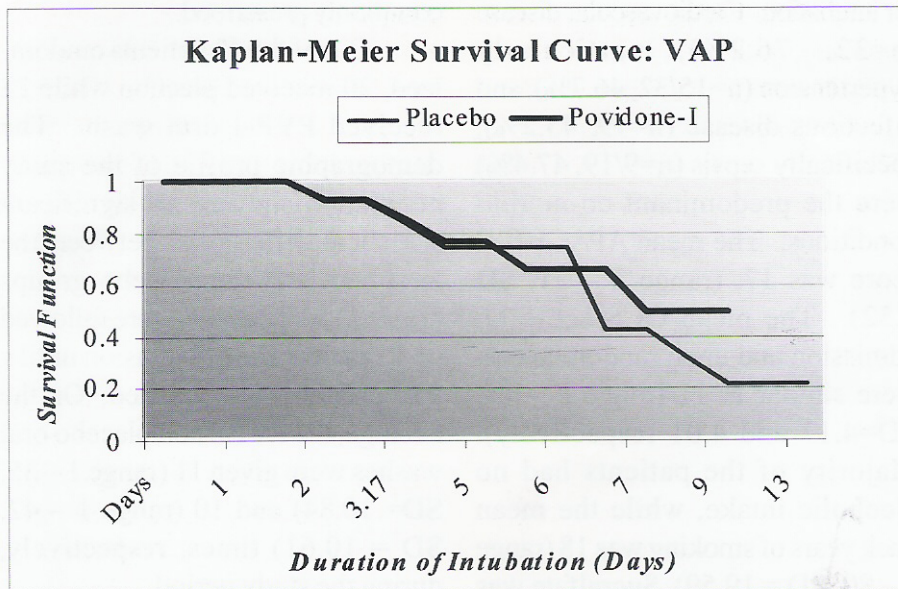


Figure 1
VAP incidence among PVP-I and placebo groups (N=42) Secondary outcomes

Of the 28 patients who did not develop VAP; 9 were discharged, 17 expired, and 2 went home against advice. Of the 14 patients who developed VAP, 8 were eventually discharged, went home against advice, and 5 expired. There were no statistically significant differences in the outcomes of the two groups analyzed.

The mean duration of intubation was 168 hours (range 0-264, SD=75.18) for the PVP-I group and 160 hours (range 12-312, SD=93.56) for the placebo group. The average length of stay was 7.6 days (range 1 - 24, SD=7.48) for the PVP-I group and 8 days (range 1-26, SD=9.55) for the placebo group. There was no statistically significant difference in the duration of intubation and ICU stay between the PVP-I group and the placebo group (Table 3).

Table 3
Secondary outcomes among PVP-I and placebo groups (N=42)

Duration	Treatment	Control	Difference	p-value
Length of Intubation (hrs)				
Mean	167.8	160.1	-7.7	0.91
95% Confidence interval			-139.5 – 124.1	
ICU stay (days)				
Mean	7.57	7.95	0.38	0.89
95% Confidence interval			-5.22 – 5.98	
Hospitalization (days)				
Mean	10.8	11.4	0.60	0.86
95% Confidence interval			-6.27 – 7.48	

Twenty-two out of the 42 patients died during the hospital stay, while 12 of 22 (54.5%) in the PVPI group died, and 10 of 20 (50%) in the placebo arm (Table 2). Septic shock was the most common overall cause of mortality (overall n=9/22, 40.9%; PVP-I n=5/12, 41.7%; placebo n=4/10, 40%), followed by cardiogenic shock and brain herniation. Majority (59%) of deaths occurred within 72 hours of ICU admission (PVP-I n= 7/12, or 58%; placebo n=6/10 or 60%). There were more patients without VAP who expired. Only three of the deaths (overall 13.6%; PVP-I n=2/12, 16.7%; placebo 1/10, 10%) were directly attributable to VAP. No adverse events directly attributable to PVP-I were noted.

DISCUSSION

This was the first attempt to evaluate the efficacy of PVP-1 oral wash in preventing pneumonia in intubated patients. Previous studies centered either on topical antibiotics⁷ or on chlorhexidine.^{4,9,10} Unlike previous studies where recruited patients came from the surgical ICU, majority of the subjects in this investigation came from the medical ICU.

The overall incidence of VAP in this study was 33.33%, lower than the 49% incidence of hospital acquired pneumonia among intubated patients, as reported by Berba et al in 1999. The lower overall rate of VAP in this study may reflect better nursing care in the ICU. It may also be the positive effect of reorienting the nursing staff to proper oropharyngeal care and infection control procedures in intubated patients. Whether this lower overall VAP incidence was due mainly to the mechanical act of cleansing the oropharyngeal cavity, regardless of antiseptic use, remains uncertain.

Pseudomonas aeruginosa and *Klebsiella pneumoniae* were the most common etiologic agents of VAP in this study. This was consistent with previous studies that showed *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* as the most common pathogens for VAP.¹⁴ Hence, the application of PVP-1 did not alter the expected isolates in the patients who developed

nosocomial pneumonia. However, no antimicrobial sensitivity testing was done due to financial constraints.

The significant reduction in the incidence of nosocomial pneumonia reported in previous randomized trials was not reproduced in our study. No statistically significant difference was noted in the incidence of VAP between the PVP-I and placebo groups. However, the Kaplan-Meier graph suggested a decreased development VAP from the 7th day of intubation among patients who were given PVP-I. This trend might have translated into a definite benefit if we were able to complete the computed sample size of 204 patients, whereas, this study only reached 21 % of the target sample size.

No statistically significant difference was likewise found in mortality rates, duration of intubation, or duration of ICU stay between the PVP-I and placebo groups. This was consistent with the results of the previous randomized controlled trials. Furthermore, in this investigation more deaths occurred among patients without VAP. Apparently, mortality was associated more with the APACHE-II score than with the development of VAP. The severity of the underlying diseases was the better predictor of morbidity and mortality. Another important factor to consider was the prompt and regular administration of the appropriate antibiotics for the infectious cases. However, the analysis of the effect of the latter was outside the scope of the study.

Povidone-iodine gargle solution has been known to cause yellowish discoloration of the teeth of people using this solution for more than six months. This discoloration is known to be reversible after weeks of discontinuation of its use. Other potential adverse events include allergy or hypersensitivity to the solution and its component products, and hyperthyroidism. Although the potential to cause hyperthyroidism is present due to the fact that PVP-I contains iodine, there has been no documented increase in thyroid functioning. In this study, no adverse drug reaction was directly attributable to the test solution. Three of the mortalities were directly attributed to VAP. However, there was no significant difference in the rate of VAP-associated mortalities between the placebo and the treatment groups.

CONCLUSIONS

Despite the sample size, this investigation on the use of povidone-iodine oral wash as prophylaxis against ventilator-associated pneumonia showed a trend towards benefit. There was no significant difference in terms of mortality and length of intubation, ICU stay, and hospitalization. Povidone-iodine oral prophylaxis for intubated patients was generally well tolerated.

Although present knowledge about the use of antiseptic prophylaxis in the prevention of ventilator-associated pneumonia points to benefit, this remains inconclusive. We therefore recommend that studies using a larger sample size should be done in order to determine whether this observation would indeed translate into a statistically significant clinical outcome. We recommend continuing the study until the computed sample size of 204 subjects is attained.

REFERENCES

1. Berba R, Alejandria M, Rosaros J, et al. Incidence, risk factors and outcome of hospital-acquired pneumonia in critically-ill patients at the Philippine General Hospital. *Phil J Microbiol Infect Dis* 1999; 28(2):29-38.

2. Pawar M, Mehta Y, Thurana P, Chaudhary A, Kulkarni V, Trehan N. Ventilator- associated pneumonia: incidence, risk factors, outcome, and microbiology. J Cardiothoracic Vasc Anesth 2003; 17(1):22-28.
3. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilator patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94:281-288.
4. Ferrer R, Artigas A. Clinical Review: nonantibiotic strategies for preventing ventilator associated pneumonia. Crit Care 2002; 6(1):45-51.
5. Kollef MH. The prevention of ventilator-associated pneumonia. N Engl J Med 1999; 340(8):627-634.
6. Kollef MH, Siver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 1995; 108:1655-1662.
7. Bergmans DC, Bonten MJ, Gaillard CA, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study." Am J Respir Crit Care Med 2001; 164(3):382-389.
8. Genuit T, Bochicchio G, Napolitano LM, McCarter RJ, Roghman MC. Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. Surg Infect 2001; 2(1):5-18.
9. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse I reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. Am J Crit Care 2002; 11(6):567-70.
10. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and non-prophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996; 109:1556-1561.
11. Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. Dermatology 2002; 204 Suppl :37-41.
12. Summers AN, Larson DL, Edmiston CE, Gasoin AK, Denny AD, Radke L. Efficacy of preoperative decontamination of the oral cavity. Plast Reconstr Surg 2000; 106(4):895-900; quiz 901.
13. Masaki H, Yoshimine H, Degawa S, et al. [Importance of a cleaning in upper airways by using Povidone-iodine for the prevention of nosocomial pneumonia.] Kansenshogaku Zasshi 2001; 75(2):97-102.
14. Crouch Brewer S, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Chest 1996; 109:1019-1029.

APPENDICES

APPENDIX A Primary Diagnosis upon ICU Admission

Primary Diagnosis	Treatment	Control	Total
Community-acquired pneumonia	8	6	14
Cerebrovascular infarction	2	2	4
Acute myocardial infarction	1	2	3
Intracranial mass	1	2	3
Cerebrovascular bleed	1	1	2
Pulmonary embolism	0	2	2
Sepsis	1	0	1
Congestive heart failure	1	0	1
Gunshot trauma	1	0	1
Bacterial Meningitis	1	0	1
Hypokalemia	1	0	1
SAH, ruptured aneurysm	1	0	1
Bleeding peptic ulcer	1	0	1
Hypovolemic shock	1	0	1
Abdominal aortic aneurysm	1	0	1
Uremia, renal failure	0	1	1
Pulmonary carcinoma	0	1	1
Hepatic encephalopathy	0	1	1
Chronic obstructive pulmonary disease	0	1	1
Bronchial asthma	0	1	1

APPENDIX B Indication for Intubation

Indications	Treatment N=22	Control N=20	Total N=42
Impending respiratory failure	10	9	19
Ventilatory support for neurologic causes	6	4	10
Pre-operative	5	3	8
CP arrest	1	2	3
Ventilatory support for respiratory muscle	0	2	2

**APPENDIX C
Etiology of VAP**

Pathogens	Treatment n=6	Control n=8	Total
Pseudomonas	4	3	7 (54%)
Klebsiella	2	3	5 (38%)
Acinetobacter	0	1	1
Escherichia coli	0	1	1
Enterobacter	1	0	1
Streptococcus group B	0	1	1
Normal flora	0	1	1
No growth	0	1	1

**APPENDIX D
Table on Final Outcome of Patients**

Final Outcomes	Treatment n=22	Control n=20	Total N=42
Home, no event	5	4	9
Home, VAP	3	5	8
Died, no event	9	8	17
HAA	2	1 ^a	3
Died (event related), VAP	2	1	3
Died (not event related), VAP	1	1	2

^a This patient who went home against advice (HAA) developed VAP.

**APPENDIX E
Causes of Mortality**

Causes	Treatment	Control	Total
VAP related	2 (20%)	1 (8%)	3 (14%)
Septic Shock	2	1	3
NOT VAP related	8 (80%)	11 (92%)	19 (86%)
Septic shock	3	3	6
Cardiogenic shock	2	3	5
Brain herniation	1	1	2
Hemorrhagic shock	0	2	2
Multiple organ failure	0	1	1
Fulminant hepatitis	0	1	1
Mechanical ventilator failure	1	0	1
Acute myocardial infarction	1	0	1

**APPENDIX F
Association of VAP and Mortality**

Outcome	VAP (n=14)	No VAP (n=28)	Fisher's Exact p-value
Number of patients who died	5	17	0.192
Mortality in percentage (%)	35.7	60.7	