Relationship between Periodontal Status and Ventilator-Associated Pneumonia

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Abstract

Objective: This study tested the hypothesis that a relationship exists between periodontal disease status and ventilator-associated pneumonia (VAP) in patients admitted to an intensive care unit (ICU).

Materials and methods: The periodontal status of 60 individuals admitted to the ICU of the Dutra University Hospital was determined, including measurement of visible plaque, gingival bleeding, and clinical attachment level. Data were analyzed by Chi-square or Fisher's exact tests, unpaired Student's *t*-test and multivariate logistic regression.

Results: Patients with VAP showed higher prevalence of periodontitis (25%) than those in the control group (12.5%), but without statistical difference ($p = 0.22$). After multivariate analysis, risk factors for ventilator-associated pneumonia included diabetes mellitus (OR = 27.76, 95% CI = 1.95-393, $p = 0.014$), and mechanical ventilation for longer than 10 days (OR = 12.1, 95% CI = 1.65-87.9, $p = 0.014$).

Conclusion: Within the limits of this study, no association between periodontitis and ventilator-associated pneumonia was found. The presence of diabetes and invasive mechanical ventilation duration (> 10 days) were risk factors for pneumonia even after the adjustment of variables.

Keywords: Intensive care units, pneumonia, periodontal diseases

Introduction

Studies have suggested that bacteria of the mouth, especially those involved in periodontal disease, play an important role in the etiology of other diseases, including respiratory diseases (Azarpazhooh and Leake, 2006; Nonnenmacher *et al.*, 2007; Sharma and Shamsuddin, 2011; Öztekin *et al.*, 2014). Periodontal disease has an inflammatory nature whose main etiologic agent is the presence of biofilm (Hajishengallis and Lamont, 2012; Lang, 2014). It is estimated that 1 mm^3 of biofilm contains approximately 100 million bacteria (Munro and Grap, 2004). The amount of biofilm increases over time and the presence of periodontal pathogens inside the biofilm in patients admitted to intensive care units (ICUs) may be a reservoir of microorganisms associated with pneumonia (Oliveira *et al.*, 2007).

Four possible mechanisms may explain the biological plausibility of the relationship between oral conditions and respiratory infections: 1) aspiration of pathogens within the mouth (from either periodontal or respiratory diseases or both); 2) modification of the mucosa of the respiratory tract that promotes adhesion and colonization by respiratory pathogens; 3) destruction of the salivary pellicle that protects against pathogenic bacteria by hydrolytic enzymes produced by periodontal pathogens;

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and 4) release of cytokines by inflamed periodontal tissues that may alter the respiratory epithelium and promote colonization by respiratory pathogens (Scannapieco, 1999; Azarpazhooh and Leake, 2006; Nonnenmacher *et al*., 2007; Siempos and Falagas, 2007). These potential mechanisms have been supported by studies showing that changes may occur in the oral microbiome during mechanical ventilation, with colonization by potential VAP pathogens (Sands *et al*., 2016; Sands *et al*., 2017). Futhermore, routine oral care methods in mechanically ventilated patients may reduce bacteria on the tongue and in saliva (Hayashida *et al*, 2016).

The main entry route of oral pathogens in the lower respiratory tract is during the aspiration of secretions from the oropharynx, occurring in approximately 70% of the patients admitted to ICUs (Munro and Grap, 2004). Ventilator-associated pneumonia ocurrs 48 - 72 h after endotracheal intubation and mechanical ventilation. VAP is classified as early, when occurring before the fourth day of intubation and mechanical ventilation onset, or late, when occurring after the fifth day of intubation and mechanical ventilation onset (Siempos and Falagas, 2007).

Most cases of pneumonia in the ICU are VAP, ranging from 8-38% of patients on mechanical ventilation (Guimarães and Rocco, 2006; Chastre and Fagon, 2007). The mortality rates of these infections may vary from 24% to 76% of cases, especially when pneumonia is associated with either *Pseudomonas ssp.* or *Acinetobacter ssp.* (Cavalcanti *et al*., 2005; Cutler and Davis, 2005). Individuals admitted to ICUs often exhibit an improper immunologic response. Additionally, the reduction of salivary flow and natural mouth cleansing together with deficient oral hygiene measures enhance bacterial colonization of the oral cavity by respiratory pathogens (Souto *et al*., 2014).

Few studies have investigated the association between periodontal disease and VAP. Bágyi *et al.* (2006) found a positive association between these two diseases by observing that the relative risk for pneumonia was 3.5 times greater in patients exhibiting the worst periodontal conditions, while Scannapieco *et al.* (2009) did not find an association between these diseases. The present study aimed to verify if periodontal disease is associtated with VAP.

Materials and methods

This study was approved by the Institutional Review Board of the Federal University of Maranhão, São Luís-Ma, under protocol number 377.995. This was a case-control study conducted in adult individuals of both genders admitted to the intensive care unit of the Dutra University Hospital. The case group (n = 20) was composed of patients diagnosed with VAP and the control group (n = 40) were patients without VAP. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria for case group were individuals admitted to the ICU aged between 18 and 80 years, having at least six teeth and diagnosed with ventilator-associated pneumonia regardless of the cause of admission. The selection of control group was based on the same criteria, except the patients did not show clinical and radiographic manifestations of respiratory infection. Exclusion criteria for both groups were as follows: patients aged below 18 years and above 80 years; patients admitted with community-acquired pneumonia; patients with spontaneous ventilation; edentate patients or patients with fewer than six teeth; patients who had periodontal treatment at least six months before the study; individuals refusing to participate in the study.

After the reading and signing of the Free and Clarified Consent Form, information was collected from the patient/legal guardian about lifestyle, social-economic conditions, medical history, dental history and data of ICU admission. It is noteworthy to mention that at the time of the interview, the examiner was blinded regarding the VAP diagnosis of the patient. A periodontal evaluation was conducted by a single previously calibrated examiner. Intra-examiner reproducibility was carried out at the beginning of the examination in a sample of 10% of the patients, randomly selected, by applying the kappa test, and the intra-examiner agreement was high (>75%).

The periodontal examination was performed with the aid of a millimeter Williams periodontal probe (Trinity®). All teeth (except for the third molars) were examined at three areas in the buccal/labial surfaces: mesial, middle, and distal. The palatal/lingual surface was not examined due to the difficulty of access as these patients generally have limited mouth opening. During the periodontal examination, the following clinical parameters were observed: number of teeth, visible plaque index (VPI), gingival bleeding index (GBI: Ainamo and Bay, 1975), clinical probing depth (CPD), gingival recession (GR), and clinical attachment level (CAL; American Academy of Periodontoloy, 2003). The diagnosis of periodontal disease was determined using the classification criteria established by Gomes-Filho *et al.* (2007). Accordingly, the patients were diagnosed with periodontal disease if they had at least four teeth with one or more sites with probing depth ≥ 4 mm, attachment loss ≥ 3 mm, and bleeding on probing at the same sites.

After the periodontal examination, the examiner accessed the medical files of the study participants to verify whether the patient did (case) or did not (control) have VAP. Thus, we aimed to eliminate bias in assessing the periodontal parameters before knowing the VAP diagnosis. VAP diagnosis was determined by the medical team of the institution's ICU and based on the following criteria: presence of recent infiltrate identified in chest radiograph associated with fever, leukocytosis or leukopenia; cough or purulent sputum; bacterial growth in tracheal aspirate culture, present after at least 48 hours of hospitalization.

Data were analyzed by statistical software (SPSS 18.0, IBM, Chicago, IL, USA). The outcome evaluated was the occurrence of VAP (case or control) and the exposure variables comprised the demographic and social-economic characterization, behavior habits, comorbidities, oral hygiene habits, and variables regarding the period of hospital admission and oral health parameters (GBI, VPI, CPD, GR, CAL, and the presence of periodontal disease).

Initially, descriptive statistics were determinded using absolute and percentage frequency, means, and standard deviations. Categorical variables were compared between groups through either Chi-square or Fischer's exact tests. The numerical variables were compared between groups using unpaired Student's *t*-test, after the analysis of normality distribution through the Shapiro-Wilk test. The level of significance used was 5% ($p < 0.05$). The association measure was obtained through odds ratio (OR) at 95% confidence interval (95%CI) and used to estimate the association between the exposure variables and VAP outcome. Multivariate logistic regression analysis was applied by taking into consideration the confounding co-variables ($p < 0.05$) to obtain the adjusted association measure.

Results

A sampling of 60 patients revealed that case group (n = 20) had a mean age of 44.2 ± 19.3 while control group (n = 40) had a mean age of 42.8 ± 16.1. *Table 1* summarizes the demographic, social-economic and behavioral profile of the sample. The males represented 55% of the case group and 35% of the control group, but without statistically significant differences between them ($p = 0.138$). Concerning age range, both groups showed a greater frequency at 40-year age range. It was also noted that the percentage of either smokers or ex-smokers was greater in the case group (40%) than in the control group (17.5%), but without statistically significant differences ($p = 0.057$).

The association between comorbidities and VAP occurrence (*Table 2*) showed that only the variable "diabetes mellitus" exhibited statistically significant differences between groups ($p = 0.038$). The case group had a higher percentage of diabetic patients (20%) than did the control group (2.5%), so that diabetes showed an association approximately 10 times greater in VAP cases than in control cases (OR = 9.75, 95% CI = 1.01-94.11).

Table 1. Distribution and association of variables related to demographic and social-economic variables and behavior habits between case and control groups.

Variables	Case (n = 20)		Control (n = 40)		OR (95%CI)	*p*
	n	(%)	n	(%)		
Sex						0.138
Male	11	(55.0)	14	(35.0)	2.26 (0.75 - 6.78)	
Female	9	(45.0)	26	(65.0)	1.00	
Age range						0.581
> 40 years	12	(60.0)	21	(52.5)	1.35 (0.45 - 4.01)	
≤ 40 years	8	(40.0)	19	(47.5)	1.00	
Marital status						0.855
Not married†	10	(50.0)	21	(52.5)	0.90 (0.30 - 2.64)	
Married	10	(50.0)	19	(47.5)	1.00	
Education level						0.855
Up to complete primary education	10	(50.0)	21	(52.5)	0.90 (0.30 - 2.64)	
Above complete primary education	10	(50.0)	19	(47.5)	1.00	
Smoking						0.057
Smoker/ex-smoker	8	(40.0)	7	(17.5)	3.14 (0.93 - 10.54)	
Non smoker	12	(60.0)	33	(82.5)	1.00	
Alcoholism						0.408
Yes	4	(20.0)	12	(30.0)	0.58 (0.16 - 2.11)	
No	16	(80.0)	28	(70.0)	1.00	

†Single, divorced, widow/widower; OR, odds ratio; 95%CI, 95% confidence interval.

The hypothesis of association between the variables of ICU admission period and VAP was tested (*Table 3*). An ICU admission period ≥ 5 days exhibited an association of approximately four times greater for VAP occurrence (OR = 3.85, 95% CI = 1.24-11.96, $p = 0.016$). Fever occurrence within the admission period (OR = 26.0, 95% CI = 2.99-229.3, $p < 0.001$) and the leukocytosis diagnosed through complete blood count (OR = 6.5, 95% CI = 1.91-22.0, $p = 0.001$) were also risk factors for VAP.

Additionally, the time of invasive mechanical ventilation also exhibited statistically significant differences between groups ($p = 0.011$). A period longer than 10 days showed an association of approximately five times greater for VAP occurrence than did the period between 1 and 5 days (OR = 5.5, 95% CI = 1.27-23.7). Notwithstanding, the type of invasive mechanical ventilation did not show statistically significant differences between groups ($p > 0.05$).

Table 2. Distribution and association of variables related to comorbidity and use of medication between case and control groups.

Variables	Case (n = 20)		Control (n = 40)		OR (95%CI)	*p*
	n	(%)	n	(%)		
Hypertension						0.057
Yes	8	(40.0)	7	(17.5)	3.14 (0.93 - 10.54)	
No	12	(60.0)	33	(82.5)	1.00	
Diabetes mellitus						0.038*
Yes	4	(20.0)	1	(2.5)	9.75 (1.01 - 94.11)	
No	16	(80.0)	39	(97.5)	1.00	
Heart disease						0.333
Yes	1	(5.0)	0	(0)	-	
No	19	(95.0)	40	(100)	-	
Use of medication†						0.343
Yes	9	(45.0)	13	(32.5)	1.69 (0.56 - 5.11)	
No	11	(55.0)	27	(67.5)	1.00	

†Continuous use medication; *statistically significant difference ($p < 0.05$); OR, odds ratio; 95%CI, 95% confidence interval.

Table 3. Distribution and association of variables related to hospital admission period between case and control groups.

Variables	Case (n = 20)		Control (n = 40)		OR (95%CI)	*p*
	n	(%)	n	(%)		
Oral hygiene during admission						0.339
Yes	19	(95.0)	35	(87.5)	2.71 (0.29 - 24.9)	
No	1	(5.0)	5	(12.5)	1.00	
Admission period						0.016*
≥ 5 days	13	(65.0)	13	(32.5)	3.85 (1.24 - 11.96)	
< 5 days	7	(35.0)	27	(67.5)	1.00	
Fever (during admission)						<0.001*
Yes	8	(40.0)	1	(2.5)	26.0 (2.94 - 229.3)	
No	12	(60.0)	39	(97.5)	1.00	
Complete blood count†						0.001*
Leukocytosis	15	(75.0)	12	(31.6)	6.5 (1.91 - 22.0)	
Normal	5	(25.0)	26	(68.4)	1.00	
Type of invasive mechanical ventilation						0.138
Tracheostomy	11	(55.0)	14	(35.0)	2.26 (0.75 - 6.78)	
Endotracheal intubation	9	(45.0)	26	(65.0)	1.00	
Period of invasive mechanical ventilation						0.011*
1 to 5 days	4	(20.0)	14	(35.0)	1.00	
6 to 10 days	5	(25.0)	9	(47.5)	1.94 (0.40 - 9.24)	
More than 10 days	11	(55.0)	7	(17.5)	5.5 (1.27 - 23.7)	

†Two patients in the control group did not have complete blood count analysis during the study period; *statistically significant difference ($p < 0.05$); OR, odds ratio; 95%CI, 95% confidence interval.

Concerning the association between VAP and periodontal disease and other oral health-related variables (*Table 4*), only the last appointment to the dentist of an interval shorter than one year showed an association with VAP risk (OR = 3.66, 95% CI = 1.17-11.4, p = 0.021).

The periodontal parameters did not have statistically significant differences between groups ($p < 0.05$). We observed that control group patients exhibited highest values of pocket depth, loss of attachment, visible plaque index, and number of teeth, but without statistically significant differences (*Table 5*).

Multivariate analysis using logistic regression was used (*Table 6*) for the variables presenting p values lower than 0.05 in univariate analysis. After this procedure, the results showed that diabetes occurrence ($OR_{adjusted}$ = 27.76, 95% CI = 1.95-393, p = 0.014) and a period of invasive mechanical ventilation longer than 10 days ($OR_{adjusted}$ = 12.1, 95% CI = 1.65-87.9, p = 0.014) were still associated with VAP risk.

Table 4. Distribution and association of variables related to periodontal disease, oral health conditions, and oral hygiene habits between case and control groups.

Variable	Case (n = 20)		Control (n = 40)		OR (95%CI)	*p*
	n	(%)	n	(%)		
Periodontal disease						0.220
Yes	5	(25.0)	5	(12.5)	2.33 (0.58 - 9.26)	
No	15	(75.0)	35	(87.5)	1.00	
Gingival bleeding index						0.345
≥ 25%	5	(25.0)	6	(15.0)	1.88 (0.49 - 7.16)	
< 25%	15	(75.0)	34	(85.0)	1.00	
Brushing frequency at home						0.711
More than once per day	19	(95.0)	38	(95.0)	1.00 (0.08 - 11.73)	
Up to once per day	1	(5.0)	2	(5.0)	1.00	
Flossing						0.266
Yes	6	(30.0)	18	(45.0)	0.52 (0.16 - 1.64)	
No	14	(70.0)	22	(55.0)	1.00	
Mouthrinsing						0.432
Yes	5	(25.0)	14	(35.0)	0.61 (0.18 - 2.06)	
No	15	(75.0)	26	(65.0)	1.00	
Toothpick use						0.140
Yes	6	(30.0)	20	(50.0)	0.42 (0.13 - 1.33)	
No	14	(70.0)	20	(50.0)	1.00	
Last dental appointment						0.021*
Less than 1 year	11	(55.0)	10	(25.0)	3.66 (1.17 - 11.4)	
More than 1 year	9	(45.0)	30	(75.0)	1.00	

*Statistically significant difference ($p < 0.05$); OR, odds ratio; 95%CI, 95% confidence interval.

Table 5. Comparison of mean and standard deviation (± SD) of the periodontal parameters between case and control groups.

Variable	Case	Control	*p*
	Mean ± SD	Mean ± SD	
Number of teeth	16.5 ± 6.8	17.5 ± 5.5	0.543
GBI (%)	12.2 ± 19.7	10.4 ± 22.5	0.746
VPI (%)	10.3 ± 26.7	22.4 ± 32.9	0.134
PD (mm)	1.62 ± 0.46	1.83 ± 0.57	0.130
CAL (mm)	2.65 ± 0.97	2.92 ± 1.82	0.461

GBI, gingival bleeding index; VPI, visible plaque index; PD, probing depth; CAL, clinical attachment level

Table 6. Logistic regression analysis of association with ventilator-associated pneumonia.

Variable	$OR_{adjusted}$ (95%CI)	*p*
Diabetes mellitus	27.76 (1.95 - 393)	0.014*
Admission longer than or equal to 5 days	2.35 (0.64 - 8.57)	0.194
Mechanical ventilation longer than 10 days	12.1 (1.65 - 87.9)	0.014*
Dental appointment < 1 year	1.80 (0.46 - 7.02)	0.395
Periodontal disease	3.12 (0.26 - 36.6)	0.367

Model adjusted for variables presenting with p values less than 0.05 in crude analysis and periodontal disease. (Diabetes mellitus, admission longer than or equal to 5 days, mechanical ventilation longer than 10 days, and dental appointment, fever, complete blood count). *Statistically significant difference ($p < 0.05$).

Discussion

The results of this study found that an ICU admission period of ≥ 5 five days showed approximately a four times greater association with VAP occurrence. A similar result was demonstrated by Oliveira *et al.* (2011), who found that an admission time ≥ 5 days was of approximately ten times greater in the case group than in the control group, with statistically significant differences. These findings suggested that the longer the length of stay, the greater the probability of a patient developing VAP.

Lisboa *et al.* (2007) conducted research on the prevalence of ICU infection and found that the ICU admission time was an important risk factor for developing hospital-acquired infection. Patients with length of stay in ICU from 7 to 30 days had a significantly greater chance of developing infections. This association may be related to reduction in salivary flow. It is known that the saliva plays a significant role in maintaining oral health and its suppression/reduction increases the risk for developing opportunistic infections (Reznik, 2005). This favors the growth of Gram-negative bacteria, and, consequently, increases the risk for inhaling these pathogens (Fourrier *et al*., 1998; Russel *et al*., 1999).

Biofilm may influence the initiation and progression of pneumonia. In this case, the bacteria from oral biofilms can migrate into the respiratory tract (Paju and Scannapieco, 2007). Microbiological and epidemiological studies have long suggested a relationship between poor oral health and respiratory disease, especially in high-risk subjects (Oztekin *et al*., 2014; Sharma and Shamsuddin, 2011). Oral hygiene tends to be poor among patients in intensive care units (ICU), leading to high amounts of dental plaque containing large numbers of potential respiratory pathogens (Scannapieco *et al.,* 1992).

In this study, the oral hygiene during ICU admission and plaque index were not statistically associated with VAP. Probably this occurred because this study began just after the nurse technicians responsible for performing the oral hygiene of the patients had participated in a workshop on oral hygiene techniques taught by the dentist in charge. Thus, we believed that the nurse technicians were calibrated for executing a satisfactory oral hygiene.

Moreover, the institutional ICU protocol in oral hygiene included the use of 0.12% chlorhexidine in addition to oral hygiene three times per day. Chlorhexidine is largely employed to inhibit biofilm formation and control gingivitis by provoking alterations in bacterial retention and growth, thus reducing bacterial colonization of the teeth (Quirynen *et al.,* 2000; Yue *et al*., 2004). Scannapieco *et al.* (2003) conducted a systematic review and concluded that chlorhexidine has an effect on reducing the risk for respiratory infections. Concerning the variables related to oral health, only the last dental appointment at an interval shorter than one year showed an association with VAP risk (OR = 3.66, $p = 0.021$). The greatest frequency was observed in the case group, probably because these patients had some oral alteration already established or health condition requiring routine dental appointments.

Diabetes mellitus was a comorbidity with statistical significant differences between groups ($p = 0.038$) in VAP occurrence. This association probably occurred because diabetes is a disease associated with other chronic diseases that may impair the individual, favoring respiratory infection. Lisboa *et al.* (2007) observed that patients exhibiting chronic diseases such as diabetes had seven times more risk of infection in the ICU.

Periodontal parameters did not show statistically significant differences between case and control groups. In fact, the control group showed worse periodontal conditions regarding probing depth and clinical attachment loss. These data disagree with the findings of the study of Gomes-Filho *et al.* (2014) that observed worse conditions in the case group than in the control group with statistically significant differences for the following variables: number of sites with clinical attachment loss of 1 - 2 mm, and number of sites with probing depth ≥ 4 mm.

It is noteworthy to mention that the study of Gomes-Filho *et al.* (2014) was conducted in patients admitted in three hospital departments (ambulatory, surgical, and ICU) with a total sample size of 85 cases and 230 controls. The sample size of this present study was smaller (20 cases and 40 controls) because we evaluated only a single ICU. Moreover, the institutional ICU has only 14 beds and the turnover of patients is low, which limits the number of patients that could be included.

Porto *et al.* (2016) conducted a case-control study that analyzed whether periodontal pathogens are able to colonize endotracheal tubes of patients in ICUs. Their analysis of the systemic condition of the population showed that of 36 patients examined, 11 (31%) developed VAP, among which nine patients (82%) died. In addition, of 26 patients that did not survive, 15 (58%) were diagnosed with periodontal disease. However, as in our study, the sample size was not large enough to demonstrate a relationship between periodontal conditions and VAP.

Periodontal disease severity may have a dose-response effect on pneumonia development, although no study has proven this relationship. In this present study, the periodontal disease severity was not assessed. Notwithstanding, we observed incipient characteristics of periodontal disease that probably had contributed to the non-association between periodontal disease and pneumonia. According to Scannapieco and Ho (2001) and Hayes *et al.* (1998), there is a tendency towards an increase in clinical attachment loss when pulmonary function is reduced.

Sharma and Shamsuddin (2011), studying the relationship between respiratory and periodontal diseases, found the deepest probing depths and the greatest attachment loss in patients with respiratory disease.

Accordingly, they concluded that the most severe periodontal disease might increase the risk for pneumonia in hospitalized individuals. The rationale behind this fact is that the most severe periodontal disease may house a greater number of pathogenic microorganisms (De Marco *et al.*, 2013).

In both groups, most patients showed a gingival bleeding index lower than 25% of the evaluated sites, which corroborates the findings of Scannapieco and Ho (2001), who did not find a significant relationship between gingival bleeding and respiratory diseases. In the study of Gomes-Filho *et al.* (2009) the association between periodontal disease and nosocomial respiratory disease was only statistically significant when age, smoking, and admission period were included in the multivariate regression model. In the present study, the possible association between periodontal disease and VAP was only significant when diabetes mellitus and invasive mechanical ventilation for longer than 10 days were included in the multivariate regression model.

One study limitation is the small sample size, due to the low turnover of patients in the ICU because many patients remained hospitalized for a long period, which limited statistical power. Another limitation was that the multivariate analysis model did not include a smoking variable, which may influence as a confounding variable in the relation between periodontitis and VAP. However, the non-inclusion of this variable occurred to avoid an over-adjustment in the analysis. In this way, studies with a larger sample are necessary in order to validate the relationship between periodontal status and VAP.

Conclusion

Recent studies suggest that oral health is directly linked to systemic health. Over the last years, the studies suggested that oral bacteria, especially periodontal pathogens, may play an important role in the etiology of other diseases, including respiratory infections. The present findings do not support an association between periodontal disease and VAP. Additional studies using a larger sample size are required to further address this question.

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