ORIGINAL ARTICLE

Influence of preoperative hospital stay in the antimicrobial resistance profile of oral microbiotic

Influência do tempo de permanência hospitalar pré-operatória no perfil de resistência a antimicrobianos da Microbiota oral

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Abstract

Objective: Verify whether there was a relationship between the occurrence of multidrug-resistant bacterial strains and the length of stay in the preoperative period. **Methods**: Clinical samples of the oral surfaces of the teeth and/or cheek mucosa were collected in the oral cavity of 37 patients who underwent elective cardiac surgery in the preoperative period from May to July 2019. The clinical samples collected were subjected to identification of colonies and antimicrobial sensitivity tests. **Results**: We observed that the patients who stayed for more than 60 days in that hospital had 17 times more likely to develop multi-resistant strains (Multi-Rs) than those that have not remained**. Conclusions**: We realized that the longer the patient stays in the hospital, the greater the chances of bacterial strains Multi-Rs. Therefore, it is important to try to reduce the length of hospital stay so that there is no increase in the occurrence of multiresistant strains in these patients

Keywords: Biofilms. Bacteria; Oral Health. Infection; Drug Resistance Bacterial.

Resumo

Objetivo: Verificar se houve relação entre a ocorrência de cepas bacterianas multirresistentes e o tempo de internação no pré-operatório. **Métodos**: Amostras clínicas das superfícies orais dos dentes e / ou mucosa jugal foram coletadas na cavidade oral de 37 pacientes submetidos à cirurgia cardíaca eletiva no período pré-operatório de maio a julho de 2019. As amostras clínicas coletadas foram submetidas à identificação de colônias e testes de sensibilidade antimicrobiana. **Resultados**: Observamos que os pacientes que permaneceram por mais de 60 dias naquele hospital tiveram 17 vezes mais chance de desenvolver cepas multirresistentes (Multi-Rs) do que os que não permaneceram. **Conclusões:** Percebemos que quanto mais tempo o paciente permanece internado, maiores são as chances de cepas bacterianas Multi-Rs. Portanto, é importante tentar reduzir o tempo de internação hospitalar para que não haja aumento na ocorrência de cepas multirresistentes nesses pacientes.

Palavras-chave: Biofilmes. Bactérias; Saúde Oral; Infecção; Resistência Bacteriana a Drogas.

INTRODUCTION

The oral cavity is a sterile human site until birth when it changes over time[1,2,3]. In the mouth, there is a diverse amount of microorganisms, including viruses, fungi, archaeans, and even protozoa, the bacterial group being the most predominant[2,4]. According to Samaranayak and Matsubara[2] (2017), the oral microbiota is formed by a wide range of microorganism species, including mandatory and optional anaerobic species. These microorganisms on tooth surfaces, gums, and mucous membranes tend to form multi-species biofilms[5]. The oral microbiota grows and increases in diversity over time until its composition reaches a balance between the resident microflora and local environmental conditions. The resident microbiota acts as a barrier to transient / exogenous organisms. Thus, the resident microbiota coexists in symbiotic harmony with the host[2,4,6]. Besides the resident microbiota, there are others that survive in the mouth only for short periods: the transitional microbiota. This includes pathogens, which are not established in the oral environment due to the protective action exercised by the resident microbiota[2].

Changes in the environment, due to changes in diet, hormone levels, and oral hygiene, for example, can break this balance[2]. The result of the host immune response can cause changes in the local environment and facilitate bacterial growth[5]. Then,

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under these conditions, this microbial balance is broken and called dysbiosis[2,7]. In hospitalized patients under mechanical ventilation, as the number of dental plaque increases, so does gingival inflammation. Several aspects make oral hygiene difficult in ICU patients due to the impossibility or difficulty of self-care, presence of the orotracheal tube, and consequent formation and growth of pathogenic biofilms. This inflammation is caused by a lack of oral hygiene, which may be a determinant of lung infection[8]. Immunosuppressed patients may be susceptible to colonization by these bacilli and acquire them through direct contact with the hands of medical staff, devices, or hospital environment[9]. Thus, within 48 hours of hospital admission, the composition of oral microbiota in critical adults may change, characterizing a dysbiosis composed mainly of microorganisms of the hospital environment, gram-negative and/or gram-positive, which colonize the oral cavity and other sites of the upper respiratory tract[8]. Thus, colonization of the oropharynx by pathogens is important for the development of respiratory infections[9,10]. The replacement of the normal oropharyngeal flora by bacteria from the hospital environment occurs by aspiration of oropharyngeal secretions from the upper respiratory tract, implemented by the decrease in the host's defense mechanisms, which are responsible for hospital pneumonia[11]. Thus, there is previous oral migration by *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with hospital-acquired pneumonia[12]. According to Marino and collaborators[13] (2017), recent evidence has indicated that dibiosis may occur in the dental plaque of patients with mechanical ventilation. According to Scannapieco and collaborators[14] (2009), the microorganisms in dental plaque of patients under mechanical ventilation are genetically identical to the strains of bronchoscopic cultures collected at the time of suspected pneumonia. Thus, it is believed that dental plaque can be an important reservoir of microorganisms causing infections[13, 14, 15, 16].

Although the mechanisms of colonization by these microorganisms in immunosuppressed patients have not yet been fully clarified, studies suggest that the etiology of oral and oropharyngeal colonization is multifactorial[10, 17]. Long-term antimicrobial treatment is a factor that causes suppression and breakdown of resident plaque resistance, which leads to excessive growth of drug-resistant external microorganisms[2]. Infections caused by multidrug-resistant strains represent a major problem, as they make the choice of therapy difficult, compromising patient recovery and increased mortality, length of stay, and health costs 18. Long-term antimicrobial treatment in hospitalized patients is a factor that causes suppression and breakdown of resident plaque resistance, which leads to excessive growth of drug-resistant external microorganisms[2]. The knowledge about the evolutionary character of the microbiota of patients during the period of hospitalization has advanced in the current decade with the new molecular technology in the field of research. Publications in journals reinforce that, in the first 48 hours after hospital admission, a phenomenon of translocation of microorganisms from the hospital environment and among patients occur. Multi-resistant microorganisms can be transmitted, in a cross-over way, between patients. In this respect, the importance of the shortest possible length of stay of the patient in the preoperative period is reinforced. In spite of the disclosure of this knowledge, Brazilian hospitals still face problems with high preoperative permanence, mainly in respect to the impact of the increased frequency of infections by multi-resistant microorganisms in patients submitted to elective surgeries.

The objective of this study is to provide evidence of the direct relationship between the preoperative stay and the presence of multi-resistant bacteria in the oral microbiota, to strengthen the importance of prevention of oral cavity dysbiosis in these patients, and to encourage the improvement of processes in order to contribute to control the spread of bacterial resistance.

METHODS

An observational, cross-sectional study was performed, approved by the Ethics and Research Committee of that hospital, under protocol 3,101,369. From May to July 2019, patients over 18 years of age were selected who would undergo elective heart surgery and would be transferred to the postoperative Intensive Care Unit (ICU). Patients under 18 years of age were excluded, or who were already under mechanical ventilation prior to surgery, or with VAP or with tracheobronchitis, or patients who had their initial collection but had their surgeries cancelled.

The sample calculation was based on the study by Souza et al 19, which observed an increase in the frequency of Streptococcus spp. in patients with aspiration pneumonia compared to patients who did not develop this condition; it is estimated that it is necessary to evaluate 35 patients in order to obtain a sample that represents, with 80% power and 95% confidence, the alternative hypothesis of this work (Kesley's method).

After signing the informed consent form, oral clinical specimen collections were always performed by a single dentist. The methodology of collecting the material and characterizing the sample was based on the methodology used in the article by Hong and collaborators[20] (2018). Biofilm samples were collected from the supra and subgingival vestibular faces of 37 patients using calibrated and disposable plastic inoculation loops.

The tooth to be collected was based on the absence criterion: 1) Second right lower molar; 2) Second left lower molar; 3) Upper right canine; 4) Upper left canine; 5) Right lower central incisor; 6) Left lower central incisor; 7) Right side jugal mucosa, in the case of edentulous patients 20. Inspection of bacterial growth of the plaques was performed after 48 hours of incubation in an incubator at 35oC.

The plaques were inspected in order to characterize the isolated colonies in terms of morphology, size, texture, edges, and pigments. Colonies with different morphological characteristics were identified by MALDI-TOF methodology using VITEK MS®

(bioMeriéux) equipment. The quality control was performed according to the recommendations of the equipment manual. Isolated colonies were subjected to antimicrobial sensitivity testing, and the minimum inhibitory concentration was determined for each microorganism/antimicrobial combination using the Biomerieux VITEK equipment.

Fisher exact test and chi-square teste were used to evaluate risk factors for any multiresistant bacteria and additionally multinomial logistic regression. All analyses were performed, adopting a 95% confidence in the Statistical Package for the Social Sciences (SPSS) software for Windows.

RESULTS

In our study, we collected clinical specimens from 37 patients (figure 1). The absolute frequencies of strains for each patient, expressed in parentheses: *Streptococcus gordoni* (14), *Streptococcus oralis* (15), Enterococcus faecalis (7), *Klebsiella pneumoniae* (8), *Serratia marcescens* (6), *Staphylococcus aureus* (3), Staphylococcus *epidermidis* (21), Staphylococcus spp. (3), *Pseudomonas aeruginosa* (7), *Streptococcus mutans* (18), *Staphylococcus capitis* (21), *Staphylococcus cohnii* (18), *Streptococcus anginosus* (18), *Streptococcus spp*. (6), *Leuconostoc* (6) Coagulase-negative staphylococci (SCN) (2), *Streptococcus mitis* (37) and *Enterobacter cloacae* (1). Of the 37 patients, 8 (21.62%) developed resistance to multiple drugs (table 1).

Figure 1. Bacterial strains in the oral cavity of patients submitted to the study

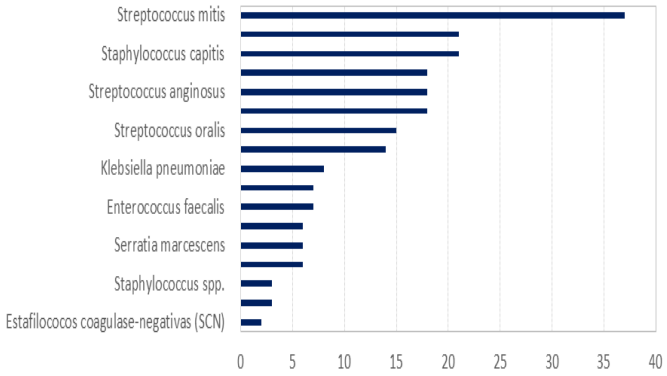

Table 1. Stratification of strains with regard to resistance profile

Multi-Rs strains	Number of patients	Resistance profile
Serratia marcescens	01	ESBL
Klebsiella pneumoniae	02	KPC; ESBL
Enterobacter cloacae	01	ESBL
Staphylococcus aureus	01	MRSA
Staphylococcus cohnii	02	MRSA
Staphylococcus capitis	02	MRSA
Staphylococcus epidermidis	01	MRSA
Total	10	

The multidrug-resistant strains found were: *Serratia marcescens* (1), *Klebsiella pneumoniae* (2), E*nterobacter cloacae* (1), *Staphylococcus aureus* (1), Staphylococcus *cohnii* (2), Staphylococcus *capitis* (2), and S*taphylococcus epidermidis* (1). Of these eight patients, three had more than one multidrug-resistant strain. The resistance mechanisms presented were: *Klebsiella pneumoniae* Carbapenemase (KPC), Beta-Lactamase Extended Spectrum (ESBL), and MRSA production.

The sample was characterized with respect to gender, age, collection site, collection topography, and jaw collection (Table 2). Tables 3 refer to the relationships between sensitivity profile and preoperative hospital stay (15 to 30 days, over 30 days, less than 60 days, and over 60 days), performed using the chi-square test. According to Table 2, all eight Multi-Rs strains appeared in a period of hospitalization longer than 30 days. In this analysis, the occurrence of a case of multi-resistant strains in a period between 30 and 60 days was perceived. However, there were seven cases of multi-resistant strains in a period longer than 60 days. In the latter case, it can be seen that the longer the length of hospital stay (over 60 days), the greater are the chances of occurrence of Multi-Rs strains. According to the previous tables, it was observed that the variable length of stay (>60 days) has a great relationship with the occurrence of Multi-Rs strains.

Table 2. Stratification of the sample with respect to sex variants, age, collection site, topography of collection and jaw collection

Variables	n	%	Multirresistência				p-Valor
			Não		Sim		
Sex							
Female	21	56.8%	17	58.6%	4	50.0%	0.663
Male	16	43.2%	12	41.4%	4	50.0%	
Age							
Up to 60 years	18	48.6%	14	48.3%	4	50.0%	0.931
>60 years	19	51.4%	15	51.7%	4	50.0%	
Collection site							
Toothless	13	35.1%	12	41.4%	1	12.5%	0.130
Toothed	24	64.9%	17	58.6%	7	87.5%	
Topography collection							
Jaw	4	10.8%	3	10.3%	1	12.5%	0.310
Jaw	20	54.1%	14	48.3%	6	75.0%	
Mucosa Jugal	13	35.1%	12	41.4%	1	12.5%	
Maxillary collection							
Previous	14	58.3%	10	58.8%	4	57.1%	0.939
Later	10	41.7%	7	41.2%	3	42.9%	
Length of Hospitalization							
Until 15 days	4	10.8%	4	13.8%	0	0.0%	0.114
16-30 days	7	18.9%	7	24.1%	0	0.0%	
≥ 30 days	26	70.3%	18	62.1%	8	100.0%	

Variables	n	%	Multirresistência				p-Valor
			Não		Sim		
Hospitalization period							
≤ 60 days	18	48.6%	17	58.6%	1	12.5%	0.042
≥ 60 days	19	51.4%	12	41.4%	7	87.5%	
Total	37	100.0%					

*p<0,05, Fisher's exact test ou chi-square test.

Table 3. Multinomial logistic regression - odds ratio (OR) for multiresistance

	p-Value	OR Adjusted (IC 95%)
Multi-resistant strains		
Sex	0.063	-
Age	0.371	-
Collection site	0.425	-
Topography collection	1.000	-
Maxillary collection	1.000	-
Hospitalization time (>60 days)	0.044	17.10 (1.08-270.89)

*p<0.05, multinomial logistic regression; OR = odds ratio; 95% CI = 95% confidence interval of Adjusted OR.

Thus, in the multinomial logistic regression and odds ratio (OR) (table 3), the length of stay greater than 60 days was a determining factor for the occurrence of Multi-Rs strains with a value of p=0.044 and OR=17.10. This data was statistically significant, and also showed that patients who stay for more than 60 days in this hospital will have 17.1 times more chances of developing multi-resistance than those who do not.

DISCUSSION

Methicillin-resistant *Staphylococcus aureus* is the most important cause of healthcare-associated infections worldwide 18. EPI usually develops in the first two to five days after intubation (early-onset EPI) and is most likely caused by antimicrobial sensitive bacteria such as methicillin-sensitive *Staphylococcus aureus* and has a better prognosis 13,21. Late-onset VAP (five or more days after the onset of mechanical ventilation) is usually related to multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and extended-spectrum b-lactamase (ESBL) produced by Enterobacteriaceae 21,22 and has been associated with increased morbidity and mortality 21. In our study, we found 1 strain of Serratia marcescens, 1 strain of *Staphylococcus aureus* resistant to multiple drugs, which, according to these authors, are involved with the etiology of VAP, deserving important attention regarding its presence in the dental plaque of these patients.

Klebsiella pneumoniae, a producer of ESBL, can cause severe infections such as bacteremia, pneumonia, and urinary tract infection, especially in critically ill patients 23. These infections seem to be more common in older patients with comorbidities and malnourished. Increased incidence of Klebsiella pneumoniae + ESBL cultivated in the urine of patients who have a long stay in healthcare facilities has also been reported. However, the emergence of Klebsiella pneumoniae strains that produce Klebsiella pneumoniae carbapenemases (KPC) has become a significant public health and clinical problem. Thus, treatment options are limited 24. In our study, two strains of Klebsiella pneumoniae were found to be multi-resistant to Klebsiella Pneumoniae Carbapenemase (KPC) and Beta-Lactamase Extended Spectrum (ESBL), which highlights the need for strategies to reduce the spread of these multidrug-resistant strains in the hospital environment, given the limited treatment options.

According to Ferreira and collaborators 1 (2017), hospital stay increases the risk of colonization by multidrug resistant enteric bacilli, information that corroborates the results obtained in this work, since, of the eight patients who developed resistance to multiple drugs, four had more than one multidrug resistant strain (Serratia marcescens (01), Klebsiella pneumoniae (02), Enterobacter cloacae (01)).

Toptas and collaborators 25 (2018) developed a study, whose objective was to identify and categorize the factors associated with long ICU stays. For this, 3925 patients and their clinical, diagnostic, and physiological variables, mortality, and length of stay were retrospectively analyzed. The mean length of stay in the intensive care unit was 10.2 ± 25.2 days. These data do not corroborate our work, since 51.4% of patients had a length of stay of up to 60 days and 48.6% more than 60 days.

The study had limitations: 1 some patients were admitted the day before surgery, and others were waiting for stabilization of their conditions; 2 patients who were valvulopaths received care prior to surgery in the dental sector of the hospital; the other patients did not; 3 due to financial limitations, we did not collect material from all patients on the day they were admitted to the hospital for comparison purposes and then 24 hours before surgery; 4 due to financial limitations, the study was conducted over a period of three months.

CONCLUSIONS

It is concluded that, the longer the patient stays in hospital, the greater are the chances of developing multidrug-resistant strains, that is, individuals who stayed for more than 60 days would have approximately 17 times more chance of developing multi-Rs to antimicrobial microorganisms. Thus, it is essential to remove dental plaque in these patients, reinforcing the need for the dentist in the ICU. It is further concluded that, despite several studies already found in the literature, further research is needed to provide definitive evidence on the relationship between the length of hospital stay and oral colonization by Multi-Rs strains.

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