Dental care before cardiac valve surgery: Is it important to prevent infective endocarditis?

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ABSTRACT

Background: Infective endocarditis (IE) is a serious disease that affects the surface of the endocardium. The spread of microorganisms from the oral cavity has been associated with the occurrence of IE.
Objective: To analyze whether dental treatment before cardiac valve surgery (CVS) influenced the occurrence of IE.
Methods: We performed a retrospective analysis of the medical and dental histories of patients undergoing CVS from 2004 to 2014. The sample consisted of 481 patients who underwent CVS divided into two groups: patients submitted to dental treatment prior to CVS (n = 110) and patients undergoing CVS without dental treatment (n = 371).
Results: Of the total sample, 38 patients (8%) were diagnosed with IE. No significant difference was detected (p = 0.496) in comparing the occurrence of IE in the group with dental preparation (6.4%) and without dental preparation (8.4%). The logistic regression model confirmed that dental treatment did not change the IE risk (p = 0.504) and indicated that age (p < 0.003) and gender (p = 0.013) were significant risk factors for IE. There was a high demand for dental procedures in the group receiving dental preparation, with no significant differences between the patients with or without IE. Hemoculture indicated qualitative differences in comparing patients with and without dental treatment, especially in the frequency of *Staphylococcus* and *Streptococcus*.
Conclusions: The results did not allow for the determination of the impact of dental treatment before CVS on IE outcomes. However, it was not possible to exclude the potential beneficial effects of dental treatment in the prevention of IE.

1. Introduction

The spread of microorganisms from the oral cavity to other sites has been associated with the occurrence of systemic diseases such as infective endocarditis (IE) [1–4]. IE is a severe disease that affects the surface of the endocardium [5–7], occurring more frequently in the vicinity of acquired or congenital heart defects [8–10]. The pathogenesis of IE has been associated with the occurrence of bacteremia, the source of which can include periodontal infection sites [11–16], dental and/or oral tissues manipulation [4,8,17–19] and even daily lifestyle habits (*e.g.*, brushing and flossing) [8,20,21].

In the presence of infection, tooth-supporting tissues became highly vascularized and enter into an intimate relationship with microbial biofilm, increasing the risk of bacteremia [3,15,22]. Surmounting evidence has indicated that dental treatment in patients at risk of developing IE could be beneficial because the elimination and/or control of acute or chronic oral infections can reduce the source of microorganisms and consequently the likelihood of bacteremia [8,11,12,14]. However, the costs and benefits of dental intervention prior to cardiac valve surgery (CVS) have not been well defined. One study demonstrated an increased risk of adverse cardiac events, including a 3% likelihood of death when dental extraction was performed before cardiac surgery [23]. Another study showed no difference in the incidence of IE or other cardiac complications in patients who underwent dental surgery concomitantly with CVS [24]. In contrast, a higher incidence of IE was previously noted in the treated group (5.4%), compared to the group

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that did not receive (1.9%) dental treatment before valve surgery [25]. Therefore, if dental intervention before CVS is beneficial in preventing post-operative IE requires further investigation.

Recently modifications were introduced to the international recommendations on IE prevention concerning dental procedures [26–28]. These modifications have exacerbated discussions and controversies in the literature concerning the associations between oral infection and dental treatment *versus* IE. Because dental infection potentially induces bacteremia and consequently IE, we evaluated here the potential effects of dental treatment performed before CVS on overall IE outcomes.

2. Materials and methods

2.1. Study design

A retrospective analysis of medical records of patients who underwent cardiac valve surgery from June 2004 to May 2014 was performed at the Hospital das Clínicas of the Universidade Federal de Minas Gerais. This study was approved by the Institutional Ethics Committee (Protocol 24287014.9.0000.5149). Patients aged 18 years old or older who underwent cardiac valve surgery and who were submitted or not to dental treatment before the procedure were included in this study. We excluded patients younger than 18 years old, patients with pacemakers, those with indefinite diagnoses of infective endocarditis (IE) and patients whose medical records had no information about the clinical data of interest.

2.2. Infective endocarditis diagnosis

The criteria for the IE diagnosis were defined by the Duke group [17, 19,27]. Data collected included age, sex, hospitalization duration, presence of diabetes mellitus, systemic arterial hypertension, acute myocardial infarction, cerebrovascular accident/transient ischemic attack (stroke), chronic renal failure, smoking habit, previous cardiac surgery, rheumatic fever and death. The variable mortality was stratified as up to 30 days after CVS and >30 days until one year after CVS. Data from hemoculture from patients with IE were also obtained.

2.3. Dental treatment

Dental evaluation consisted of anamnesis and clinical and radiographic examinations. Oral mucosa, teeth, gums and alveolar bone were evaluated. This evaluation aimed to identify infectious foci, such as caries, periodontal and endodontic disease. Patients submitted to invasive dental procedures received antibiotic prophylaxis following AHA recommendations (2014) [26]. Data on the type of dental procedure performed were collected: coronal polishing, scaling and root planning, restorative procedures, endodontic treatment, extractions, biopsies, abscess drainage and hemorrhage control. The number of appointments dates of the beginning and end of dental treatment and whether the dental treatment was considered completed or not before surgery were recorded.

2.4. Statistical analysis

Data analysis involved the description of frequencies for the categorical variables according to the response variable 'IE' and the main explanatory variable 'preoperative dental care', with the chi-square test used to determine associations between these variables. Because the scale variables did not have a normal distribution (Kolmogorov–Smirnov test <0.05), the Mann–Whitney test was used to compare the two independent groups in the measurement of these variables. A multivariate binary logistic regression model was constructed, estimating odds ratios (ORs) for IE and respective 95% confidence intervals (CIs) for the groups of patients with and without preoperative dental care,

adjusted according to other independent variables. Covariates with p-values <0.20 in the bivariate analysis were incorporated into the model, which was built by the 'enter' method. Variables that remained significant (p < 0.05) after adjustments were maintained in the final model. The covariates 'previous cardiac surgery' and 'rheumatic fever' were included and retained in the model for adjustment regardless of their p-values because the groups that received preoperative dental care or not differed with regard to these variables at baseline. Similarly, 'preoperative dental care' was forced into the model because it was the variable of interest. The Hosmer and Lemeshow test was used to assess the model fit. A multivariate multinomial logistic regression model was also constructed, similar to that having 'mortality' as the outcome variable.

All of the statistical analyses were performed using the SPSS™ statistics software (SPSS for Windows, version 20.0, SPSS Inc., Chicago, IL, USA), and the level of significance adopted was 5%.

3. Results

A total of 481 records of patients who underwent cardiac valve surgery between 2004 and 2014 were analyzed. Of the total, 371 patients (77%) did not receive dental treatment, and 110 patients (23%) underwent dental preparation before CVS.

A comparative analysis was performed between the groups with and without dental preparation, and no significant difference was observed in the sex distribution (p = 0.191). The number of patients with smoking habits was also similar in both groups (p = 0.504). Patients who underwent dental treatment were younger (p = 0.032) and had a higher percentage of previous cardiac surgeries (p = 0.032) than the group without dental preparation (Table 1).

The comparison between the groups with and without dental preparation concerning principal diagnosis showed similar rates of diabetes mellitus (p = 0.104), systemic arterial hypertension (p = 0.756), acute myocardial infarction (p = 0.773), cerebrovascular accident (p = 0.923) and chronic renal failure (p = 0.609). There was a significant difference in the occurrence of rheumatic fever (p < 0.001), which was more frequent in the group with dental preparation (53%) than in the group without dental preparation (21%) (Table 1). The hospitalization duration in the group that underwent dental treatment (Md = 21.5 days) was significantly longer than in the group without dental preparation (Md = 14.0 days) (p < 0.001).

Of the total sample, 38 patients (8%) were diagnosed with IE. The results showed no significant difference (p = 0.496) between the occurrence of IE in comparing the group with dental preparation (6.4%) and

Table 1
Demographic data and principal diagnosis of patients who underwent cardiac valve surgery considering dental preparation before surgery.

Variables	Dental treatment		p-Value
	Yes	No	
Female	56 (51.0%)	215 (58.0%)	0.191[a]
Male	54 (49.0%)	156 (42.0%)	
Age (years)	47.3 ± 15.5 (Md = 48.5)	51.2 ± 16.4 (Md = 53.0)	**0.032**[b]
Smoking habit	16 (15.0%)	45 (12.0%)	0.504[a]
Previous cardiac surgery	38 (35.0%)	90 (24.0%)	**0.032**[a]
Diabetes mellitus	8 (7.0%)	48 (13.0%)	0.104[a]
Systemic arterial hypertension	57 (52.0%)	186 (50.4%)	0.756[a]
Acute myocardial infarction	6 (5.0%)	23 (6.2%)	0.773[a]
Cerebrovascular accident	8 (7.0%)	28 (7.6%)	0.923[a]
Chronic renal failure	8 (7.0%)	22 (5.9%)	0.609[a]
Rheumatic fever	58 (53.0%)	78 (21.0%)	<**0.001**[a]

Md: median. p values less than 0.05 appear in bold.
[a] Chi-square test.
[b] Mann-Whitney.

the group without dental preparation previous to cardiac valve surgery (8.4%) (Table 2). Comparing the groups with and without IE, significant differences were observed in the following variables: sex and age. IE was more frequent in men (11.0%) than women (5.5%) (p = 0.029), and patients with IE were significantly younger (p = 0.011) than the group without IE. Smoking habits (p = 0.804) and previous cardiac surgery (p = 0.137) were similar in the groups with and without IE (Table 2).

Regarding the IE diagnosis, no differences were observed between the groups with and without IE with the occurrence of diabetes mellitus (p = 0.791), acute myocardial infarction (p = 0.068), cerebrovascular accident (p = 0.054), chronic renal failure (p = 0.283) and rheumatic fever (p = 0.513) (Table 2). Patients with IE had significantly longer hospitalization durations (Md = 42 days) than the patients without IE (Md = 15 days) (p < 0.001).

Multivariate analysis was performed to identify the factors associated with IE. In the regression logistics model for IE, dental preparation (p = 0.504, OR 1.3; 95% CI: 0.55 to 3.32), rheumatic fever (p = 0.103 OR 0.48; 95% CI: 0.20 to 1.15) and previous cardiac surgery (p = 0.077, OR 1.94; 95% CI: 0.93–4.05) did not represent risk factors for IE. In contrast, age (p = 0.003, OR 0.9; 95% CI: 0.94–0.98) and sex (p = 0.013, OR 2.4; 95% CI: 1.20–4.88) were significant risk factors for IE. Data indicated that a man had a 2.4 times greater likelihood of developing IE than a woman and that a patient up to 45 years old has 0.9 times greater likelihood of presenting with IE than a patient older than 45 years old (Table 3).

The mortality of patients with IE was 18%, and no differences were observed when comparing the groups with or without dental preparation (p = 1.00). Mortality of patients with EI occurred in 24hs after CVS (one patient that receive dental treatment before CVS); until 30 days of CVS (3 patients, none received dental treatment) and from 30 days until one year of CVS (3 patients, none received dental treatment). Thus, IE mortality was not modified by dental preparation before CVS. Similarly, age (p = 0.59), gender (p = 0.83), systemic arterial hypertension (p = 0.81), acute myocardial infarction (p = 0.22), cerebrovascular accident (p = 0.30), chronic renal failure (0.33), smoking habit (p = 0.33), previous CVS (p = 0.24) and rheumatic fever (p = 0.24) did not modify IE mortality. However, diabetes mellitus significantly increased the risk of mortality (p = 0.035).

The regression logistics model was constructed to evaluate the influence of dental treatment on overall mortality. When considering the overall mortality up to 30 days after CVS (p = 0.377, OR 1.5; 95% CI: 0.58 to 4.19) and mortality >30 days and until one year (p = 0.762, OR 0.8; 95% CI: 0.27 to 2.57), no influence of dental treatment on

Table 2
Demographic data of patients who underwent cardiac valve surgery considering the occurrence of infective endocarditis.a, b, c

Variable	Infective endocarditis		
	Present	Absent	p-Value
Female	15 (5.5%)	256 (94.5%)	**0.029**[a]
Male	23 (11.0%)	187 (89.0%)	
Age (years)	43.1 ± 17.2 Md = 36.0	50.98 ± 16.0 Md = 53.0	**0.011**[b]
Smoking habit	4(6.6%)	57 (93.4%)	0.804[c]
Previous cardiac surgery	14 (10.9%)	114 (89.1%)	0.137[a]
Diabetes mellitus	5 (8.9%)	51 (91.1%)	0.791[c]
Systemic arterial hypertension	13 (5.3%)	230 (94.7%)	**0.036**[a]
Acute myocardial infarction	5 (17.2%)	24 (82.8%)	0.068[c]
Cerebrovascular accident	6 (16.7%)	30 (83.3%)	0.054[c]
Chronic renal failure	4 (13.3%)	26 (86.7%)	0.283[c]
Rheumatic fever	9 (6.6%)	127 (93.4%)	0.513[a]
Dental treatment	7 (6.4%)	103 (93.6%)	0.496[a]

Md: median.
[a] Chi-square test.
[b] Mann-Whitney.
[c] Fisher's exact test.

Table 3
Logistic regression model considering the diagnosis of infective endocarditis.

Variable	OR	95% C.I.	p
Sex (ref → male)	2.4	1.20–4.88	**0.013**
Age (ref → until 45 years)	0.9	0.94–0.98	**<0.003**
Previous cardiac surgery (ref → yes)	1.9	0.93–4.05	0.077
Rheumatic fever (ref → yes)	0.4	0.20–1.15	0.103
Dental treatment (ref → yes)	1.3	0.55–3.32	0.504

mortality was detected. Moreover, the regression logistics model for mortality occurring 30 days after CVS revealed that diabetes mellitus (p = 0.258, OR 0.5; 95% CI: 0.16 to 1.63), chronic renal failure (p = 0.136, OR 0.36; 95% CI: 0.10 to 1.36), previous cardiac surgery (p = 0.145, OR 0.5; 95% CI: 0.19 to 1.26) and rheumatic fever (p = 0.915, OR 1.05; 95% CI: 0.37 to 2.97) were not significant risk factors. When evaluating mortality occurring after 30 days up to one year of CVS, chronic renal failure was a significant risk factor (p = 0.004, OR 0.19; 95% CI: 0.62 to 0.59), while diabetes mellitus (p = 0.092, OR 0.38; 95% CI: 0.12 to 1.17), previous cardiac surgery (p = 0.442, OR 0.6; 95% CI: 0.25 to 1.82) and rheumatic fever (p = 0.171, OR 0.4; 95% CI: 0.17 to 1.35) did not change the mortality outcome.

Data regarding the nature/type of dental procedures in patients who underwent cardiac valve surgery considering the occurrence of IE are shown on Table 4. A high demand for dental procedures, such as extractions (68.6%), periodontal treatment (49.5%), coronary polishing (39%) and restorations (32.4%), was observed. Three percent of the patients were edentulous, and 4% of the patients became edentulous postdental preparation, totaling 8.5% of the sample. It is interesting to note that no edentulous patients had IE. Of the patients with total and/or partially removable dentures, two patients required denture adjustment, two patients required Candidiasis treatment, one patient had a mucosal lesion and required biopsy, and one patient needed an extraoral abscess drained. These data suggested a poor oral health condition in patients who progressed or not to IE because there were no significant differences in dental treatment demands verified in comparing both groups (Table 4).

The patients required one appointment (35.6%), 2–3 appointments (47.1%), 4–5 appointments (12.5%) and 6 or more appointments (4.8%) to finish dental treatment. The groups with and without IE required a similar number of appointments (p = 0.826). Most of the patients (88.3%) had their dental treatment concluded. The frequency of patients who completed dental treatment before CVS was also similar in patients with and without IE outcomes (p = 1.000). In 8% of cases, dental treatment was not concluded due to the severity of systemic disease.

In the group with dental preparation, hemoculture was positive in 85.7% of the cases, compared to 83.9% in the group without dental preparation (p = 0.904). In the group of patients who underwent dental treatment, the most commonly identified organism was *Streptococcus*

Table 4
Type of dental procedure performed considering the diagnosis of infective endocarditis.a

Procedure	Infective endocarditis		
	Present	Absent	p-Value[a]
Coronal polishing	3/7 (42.9%)	38/98 (38.8%)	1.000
Restorative treatment	1/7 (14.3%)	33/98 (33.7%)	0.424
Periodontal treatment	4/7 (57.1%)	48/98 (49.0%)	0.716
Extractions	4/7 (57.1%)	68/98 (69.4%)	0.675
Endodontics	0/7 (0.0%)	1/98 (1.0%)	1.000
Edentulous	0/7 (0.0%)	9/99 (9.1%)	1.000
Denture adjustment	0/7 (0.0%)	2/98 (2.0%)	1.000
Candidiasis treatment	0/7 (0.0%)	2/98 (2.0%)	1.000
Biopsy	0/7 (0.0%)	1/98 (1.0%)	1.000
Abscess drainage	0/7 (0.0%)	1/99 (1.0%)	1.000
Hemorrhage control	0/7 (0.0%)	3/98 (3.1%)	1.000

[a] Fisher's exact test.

sp. (33.3%). In this group, a similar frequency (16.7%) of *Candida parapsilosis*, *Corynebacterium sp.*, *Enterococcus faecalis* and *Staphylococcus sp.* was identified. In the group without dental preparation, there was a predominance of *Staphylococcus sp.* (56%), followed in order by *Streptococcus sp.* (24%) and *Enterococcus sp.* (16%). Fig. 1 illustrates these data and indicates qualitative differences in the distributions of the identified microorganisms in the hemoculture of patients with IE, subjected or not to dental preparation before cardiac valve surgery. It was possible to observe a trend of wider distribution of microorganisms in the group without dental preparation. Considering the ten different groups of microorganisms identified in hemoculture, eight were positively identified in the group without dental preparation, and five were identified in the group with dental preparation.

4. Discussion

The main results of this study are described as follows: 1) dental preparation before cardiac surgery did not change the occurrence of IE. 2) The need for dental treatment was equally high in patients who developed IE or not and both groups required a similar number of attendances to complete the dental treatment prior CVS. 3) The regression logistic model confirmed that dental treatment did not change the IE risk and reveal age and gender as major risk factors for IE. 4) The hemoculture showed qualitative differences comparing IE patients who underwent dental treatment or not, with a tendency of a wider distribution of microorganisms in the group without dental preparation.

Previous data from the literature, published in the United States [11], Japan [14] and Germany [12], have indicated the benefits of dental treatment before surgical valve approaches in reducing the risk of IE. In contrast, other studies conducted in the United States [23], Sweden [25] and Spain [29] did not obtain favorable results. Comparison of the data from our study with those conducted in other countries should be performed with caution because one of the factors that can influence data is the oral health status of the population subjected to CVS in these different countries. The population that participated in this study was attended by a public health system with low access to dental care services throughout their lives. In 2004, the Brazilian National Oral Health Policy was implemented in the country, expanding the access of the general

population to dental treatment [30], but there remains a significant number of people with no access to dental services.

One important aspect of this study was that the definition of the oral health status was based on the demands. The data allowed for the consideration that all of the patients who underwent dental treatment had poor oral health conditions, based on the high demand for restorative, periodontal and tooth extraction procedures. No significant differences in dental treatment demands in the groups with and without IE were observed except for the absence of defined indices of caries [31] and periodontal conditions [31], and it was not possible to exclude oral conditions that might have influenced IE outcomes. Interestingly, no cases of IE were observed in edentulous patients.

For the results interpretation, we should bear in mind that the dental preparation before surgery possibly had probably a major impact on the removal of acute infectious foci. Consequently, chronic lesions, such as periodontal or periapical disease, should not be considered as "fully" solved after a few dental appointments and no follow-up. In this study, most of the patients required approximately one to three appointments to be considered to have completed dental treatment. Thus, the hypothesis was that, despite the majority of patients undergoing dental preparation being considered as having completed treatment, it was not possible to exclude the persistence of oral chronic infectious foci. There is no consensus regarding the time postperiodontal therapy to consider a patient free of the disease. One study demonstrated that, after non-surgical periodontal therapy, patients with severe periodontitis required 2 to 6 months for reduction in systemic inflammatory markers [32]. Therefore, a period of follow-up after dental treatment is pivotal for the achievement of a healthy oral status. This aspect is relevant for further studies evaluating the impact of dental preparation on IE outcomes.

Another important factor to be considered in interpreting the results is that bacteremia itself is not the only factor that determines the occurrence of IE, and several risk factors should also be considered [8,15,18, 26]. Multivariate analysis indicated that men up to 45 years old had significantly increased risk of developing IE, while comorbidities were excluded as risk factors in this model. The most frequent comorbidities in patients with IE were cerebrovascular accident, acute myocardial infarction and chronic renal failure. IE was more frequent in men and young adults. These patients had prolonged hospitalization durations and a higher mortality rate than the others. These demographic data were similar to other studies [7,17,19]. Prolonged hospitalization periods require high costs and increase the risk of infections [17]. In this study, it was observed that patients who underwent dental preparation had longer hospitalizations than those without dental preparation. This result might be associated with the high proportion of patients with rheumatic fever in the group that underwent dental preparation. The patients with rheumatic fever were younger and had more severe systemic conditions, which might also explain the significantly greater frequency of repeated CVS in the group with dental preparation.

The total rate IE observed (8%) was similar to that in other studies that reported 9.2% [33] and 7% to 25% [23]. The overall mortality rate in these patients was 18%, which was in agreement with other mortality rates reported between 13% and 40% [7,17,23,34]. We obtained a low rate of postoperative complications (2.9%) during dental preparation. The complications observed in our sample were related to postextraction hemorrhage due to continuous anticoagulation use in patients with mechanical valve prostheses. Our data were similar to previous studies that showed a low complication rate in pre-CVS patients when extractions were performed concomitant with or before CVS [14,24]. Conversely, one study showed a high mortality rate in pre-CVS patients who underwent dental extraction [23].

Despite the absence of significant associations between the occurrence of IE and previous dental preparation, the hemoculture data showed qualitative differences between the two groups, especially in *Staphylococcus sp.* and *Streptococcus sp.* While these hemoculture data were similar to others [6,29,35], the oral health condition of the patients
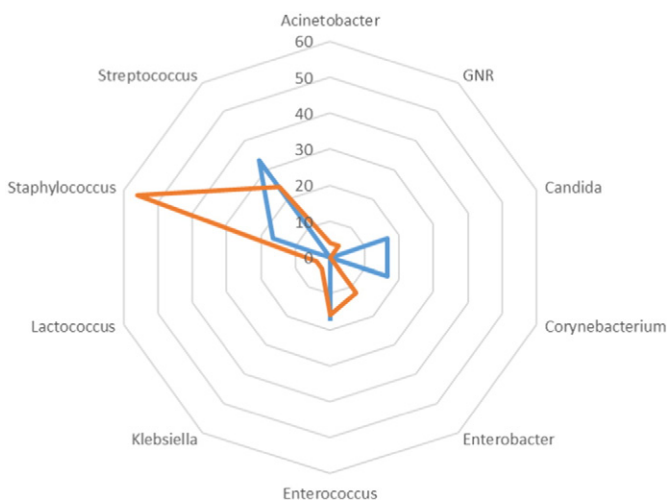
Fig. 1. Distribution of microorganisms identified in the hemoculture of patients with IE submitted or not to dental preparation before cardiac valve surgery. Microorganisms were grouped by patient gender, and the data represent the frequency of positivity in blood samples. Blue line: patients with dental treatment; Orange line: patients without dental treatment. GNR: Gram-negative rod.

has not always been included in data interpretation. The identification of *Streptococcus sp.* in this study was more common in the group that underwent dental preparation. However, only two species, *Streptococcus mitis/oralis* and *Streptococcus viridans,* were identified in this group, while five species of *Streptococcus* were found in the group without dental preparation. The data must be interpreted with caution because hemoculture results indicate the presence or absence of the determined microorganism and not the bacterial load. Furthermore, despite the oral cavity having been considered an important source of bacteremia [16], the usual routine hemoculture includes methods for cultivating strictly anaerobic microorganisms, which are prevalent in the periodontal biofilm [16]. The growing number of IE by *Staphylococcus sp.* has been associated with other sources of infection, emphasizing the skin as the main point of entry into the body, mainly due to vascular access [7,17,36,37].

There is a consensus among American (AHA), European, Australian and British (NICE) committees that the maintenance of oral health is the most important factor in reducing the incidence of bacteremia and the risk of IE in susceptible individuals [26–28]. This assumption has been based on several studies showing the occurrence of bacteremia after daily activities, such as toothbrushing and flossing, compared to those triggered by dental procedures [4,20,38,39]. One study showed that poor oral hygiene and periodontal disease resulted in significantly increased risk of bacteremia after toothbrushing [39,40]. Thus, poor oral health conditions would constitute an additional risk factor, increasing the frequency and magnitude of bacteremia as a permanent source of microorganisms. Accordingly, the potential contribution of dental treatment to the prevention of IE is unquestionable because the removal of acute and/or chronic infectious foci restores oral health with a consequent impact on the occurrence rates of bacteremia and IE. Previous studies have shown that oral care was effective in preventing IE in patients undergoing CVS [11,12,14]. In contrast, a study showed a greater number of cases of IE in the group that underwent dental treatment before cardiac surgery [25]. In this study, the observation of similar occurrence rates of IE in the groups with and without dental treatment before CVS should be interpreted in light of the aforementioned aspects such as the complexity of causal factors influencing IE outcomes and the limited power of dental treatment to solve chronic oral diseases immediately.

From the results of this study, we can suggest that chronic infectious foci, such as those with endodontic and/or periodontal causes, did not have complete resolution. The main problem raised was the probable persistence of chronic foci of infection due to insufficient time for follow-up after treatment completion. Therefore, our results do not allow for establishing a direct relationship between oral health and the occurrence of IE. However, it is not possible to exclude the potential beneficial effects of dental treatment in the prevention of IE. These data might be important to tailoring dental care programs for patients with increased IE risk.

Conflict of interest

Authors declare no conflicts of interest.

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