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Oral Hygiene and Infective Endocarditis: A Case Control Study

Running Title: Oral Hygiene and Infective Endocarditis

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Abstract

Objective: To determine if oral hygiene is associated with infective endocarditis (IE) among those at moderate risk for IE.

Study Design: This is a case control study of oral hygiene among hospitalized patients with IE (cases) and outpatients with heart valve disease but without IE (controls). The primary outcome was mean dental calculus index. Secondary outcomes included other measures of oral hygiene and periodontal disease (e.g., dental plaque, gingivitis) and categorization of blood culture bacterial species.

Results:

The 62 case participants had 53% greater mean dental calculus index than the 119 control participants (0.84, 0.55, respectively; difference = 0.29, 95% CI:0.11, 0.48; p=0.002) and 26% greater mean dental plaque index (0.88, 0.70, respectively; difference = 0.18, 95% CI: 0.01,0.36; p=0.043). Overall, cases reported fewer dentist and dental hygiene visits (p= 0.013) and fewer dental visits in the 12 weeks prior to enrollment than controls (p=0.007). Common oral bacteria were identified from blood cultures in 27 of 62 cases (44%).

Conclusions:

These data provide evidence to support and strengthen current AHA guidance that those at risk for IE can reduce potential sources of IE-related bacteremia by maintaining optimal oral health through regular professional dental care and oral hygiene procedures.

Key Words
Infective endocarditis
Bacteremia
American Heart Association
Cardiac
Plaque
Calculus
Case Control
Oral hygiene

INTRODUCTION

Infective endocarditis (IE), typically encountered as a heart valve infection, is uncommon in the general population but associated with high morbidity and mortality.[1-3] It was first suggested over 100 years ago that bacteremia from the oral cavity could cause IE.[4] This concept was later reinforced by reports that viridans group streptococci (VGS) related to oral hygiene and dental extractions caused IE.[5,6] In 1955, the first American Heart Association (AHA) guidelines on prevention of IE recommended that patients at increased risk for IE should receive antibiotic prophylaxis (AP) before a variety of invasive procedures.[7] However, in 2007, the AHA rescinded this recommendation for those considered to be at moderate risk of complications from IE, a cohort that comprises about 90% of persons with heart valve disease,[8] and recommended that AP should be restricted to those at high IE risk undergoing invasive dental procedures. These recommendations were maintained in the 2021 AHA/ American College of Cardiology guidelines.[9,10]

Historically, 20% to 54% of IE cases are caused by bacterial species common to the oral cavity.[11-13] Gingivitis, caused by the accumulation of dental plaque on the teeth, affects 50 to 90% of the world-wide population.[14] Prospective studies demonstrate an increased risk of bacteremia from minor gingival manipulations such as tooth brushing in those with increased plaque and calculus.[16,17] The vast majority of dental plaque in the healthy state involve streptococci (*e.g., S. mitis*)[18,19] and thus, dental plaque is of relevance given the prominent role of VGS as a cause of IE.[10,20]

In the healthy state, the gingival crevice around the teeth is lined by a thin, highly permeable layer of non-keratinized epithelium that separates potentially pathogenic organisms from the

general circulation (Figure 1). Accumulation of dental plaque and calculus result in bacterial growth, gingival inflammation, ulceration and greater permeability of the crevicular epithelium,[14,21-23] which likely result in increased frequency of VGS bacteremia.

There is growing evidence that frequent bacteremia from plaque and calculus is likely associated with risk of IE. In a prospective study of patients undergoing tooth extraction vs. toothbrushing, mean plaque and calculus scores were associated with increased risk for bacteremia due to common IE pathogens.[17,24,25] There is an evolving consensus that cases of VGS IE are far more likely to have occurred from routine activities of daily living (*e.g.*, toothbrushing) than from infrequent invasive dental office procedures, particularly in those with poor oral hygiene.[10]

Although maintaining good oral health has been mentioned in the AHA guidelines since at least 1972,[26] this recommendation is based largely on expert opinion and inference from 70 years of studies using bacteremia as a surrogate measure of risk for IE. The purpose of this study was to determine if plaque, calculus and other measures of oral hygiene are associated with IE among those defined by the AHA criteria to be at moderate risk for complications of IE.[27]

METHODS

Study Sample

Cases and controls age ≥18 years were recruited at a 1:2 ratio with age and each enrollment center matching from a similar geographic area surrounding four medical center study sites. Case participants were patients hospitalized with modified Duke Criteria positive IE.[28] Inclusion

criteria restricted IE cases to those who were defined as being at AHA moderate risk for IE, given persistent uncertainty in clinical practice regarding their management.[9] Potential participants were excluded if they were previously determined to be at AHA high risk or had nosocomial, health-care associated, or injection drug related IE (Appendix Table 1).[29] Cases were identified as early in their hospitalization as possible to avoid exclusion due to increased medical compromise or surgical intervention (*e.g.,* cardiac valve replacement), and to minimize the impact of hospitalization and IE management (*e.g*., systemic antibiotics) on study outcome measures of oral hygiene and gingival disease. To facilitate case enrollment, we designed a prospective electronic health record screening tool to identify potential IE inpatients soon after admission.[30]

Control participants were asymptomatic outpatients who had never developed IE but were at AHA moderate risk for IE due to pre-existing heart valve disease. They were recruited and examined in the study site outpatient echocardiography laboratories. The study protocol was approved by the Institutional Review Board at the participating institutions prior to data collection and all participants gave informed consent. Details of inclusion and exclusion criteria are given in Table 1 of the Appendix.

Study Outcomes

We chose dental calculus index score[31] (range 0-3) as our primary outcome measure based on prior studies demonstrating associations between different measures of oral hygiene, and risk of bacteremia from toothbrushing or tooth extraction.[17,24] Additionally, dental calculus is less likely to be altered by variations in diet, oral hygiene procedures or use of systemic antibiotics during

hospitalization. Secondary outcomes included: plaque index[32] (range 0-3), gingival index[32] (range 0-3), periodontal probing depth, presence or absence of bleeding on probing, and periodontal attachment loss on 6 specific "Ramfjord" index teeth.[31] Periodontal measures on these teeth have been shown to have a high correlation with measures obtained from the entire dentition.[33,34] If any of the "Ramfjord index teeth" were missing, the closest distal tooth was used as a substitute. In the absence of a tooth distal to the index tooth, the next tooth in a mesial location was measured. Molar or premolar index-teeth were never replaced by an anterior tooth. Tooth substitution has been shown not to distort estimates of oral hygiene or periodontal disease.[33] All indices and periodontal measures were obtained by trained and calibrated dental examiners. Details of the oral hygiene and periodontal disease measurements are given in Table 2 of the Appendix.

Following written informed consent, cases and controls provided the same medical and dental history information and underwent the same detailed oral examination. Demographic, social, and health history information were obtained from the participants and their electronic health record. We also obtained a history of invasive dental and other procedures in the 12 weeks prior to study enrollment. Case blood samples obtained for IE diagnosis were processed and identified by standard culture and molecular methods at each site hospital clinical microbiology laboratory according to hospital site-specific standards. Blood cultures were not obtained from control participants.

Statistical analysis

The primary outcome variable (dental calculus) was analyzed for mean difference in the calculus index and the sum calculus index between cases and controls. Exposure differences and 95%

confidence intervals (95% CI) between cases and controls were calculated. Additional multivariable regression analyses were conducted to test for possible confounding variables such as education, insurance and smoking. Secondary analyses of dental plaque, clinical attachment loss, bleeding index, pocket depth, and gingival index were conducted in a similar manner as the primary analysis. A T-test, Wilcoxon rank sum test, chi-square test, or Fisher's exact test were used to compare characteristics of cases and controls. Statistical analyses were performed using SAS Enterprise Guide version 7.1 on the platform of version 9.4 (SAS Institute Inc., Cary, NC, USA).

The planned sample size of 112 cases and 224 controls was based on prior studies,[17,24] an assumed adjusted exposure odds ratio of 2.0 for cases to controls, and a 25% prevalence of Mean Calculus Index Score ≥2 in the control group. This sample size would have a power of 0.80 with two-sided Type I error rate of 0.05. However, after enrolling 62 case and 119 control participants, the study was terminated at the end of the 5-year study period. A post-hoc power analysis demonstrated a 0.88 power for the main outcome of mean dental calculus index (two-sided Type I error rate of 0.05).

RESULTS

Study Sample

Between August 2016 and October 2019, a total of 1,050 inpatients with suspected or confirmed IE were screened and 104 were determined to be screen eligible cases (Figure 2). After

additional exclusions (n=42), 62 case participants consented and completed the study. The median time between hospital admission and study enrollment was < 24 hours. Utilizing echocardiography in the outpatient setting, 297 potentially eligible controls classified as AHA moderate risk for IE were identified. Of these, 178 were excluded either based on detailed screening, unwillingness to participate, or inability to complete the protocol after consenting, leaving 119 controls who completed the study. The statistical analysis was based on data available at the end of the study's 5-year funding period (62 cases and 119 control participants).

Demographics, social and medical history

There were no significant demographic differences between cases and controls (Table 1). Cases had significantly greater lifetime exposure to cigarettes (p=0.032), Cases also had a significantly lower frequency of dentist and dental hygiene office visits than controls (p= 0.013), significantly fewer dental office visits in the 12 weeks prior to enrollment (p=0.007) and were more likely to have never had a dentist or dental hygiene office visit (11.5% vs. 0.84%, Table 2). Additionally, in a sub-analysis of participants who had not had a dental visit in the 12 weeks prior to enrollment, cases had a significantly higher mean and sum calculus scores (p=0.004 and p=0.003, respectively) and mean and sum plaque scores (p=0.034 and p=0.037, respectively) (Appendix Table 3).

There were no significant differences between cases and controls with respect to pulmonary, coronary artery, chronic kidney or gastrointestinal disease, human immunodeficiency virus or cancer, hypertension, immunosuppressive therapy, alcoholism, diabetes, or sleep apnea (Table 2). Controls were more likely to have had congenital heart disease not considered AHA high risk (p=0.047) while cases were more likely to have features associated with IE e.g., a history of

cerebrovascular disease (cerebral vascular accident or transient ischemic attack) (p=0.002), illness requiring systemic steroids (p<0.001) or history of fever (p<0.001).

Oral health outcomes

The 62 case participants had 53% greater mean dental calculus index than the 119 control participants (0.84, 0.55, respectively; difference = 0.29, 95% CI:0.11, 0.48; p=0.002) and 26% greater mean dental plaque index (0.88, 0.70, respectively; difference = 0.18, 95% CI: 0.01,0.36; p=0.043) (Table 3). Multivariable regression showed similar findings (mean calculus index difference = 0.27, 95% CI: 0.10, 0.44; p=0.002; sum dental calculus difference = 6.0, 95% CI: 2.1, 9.9; p=0.003). Other measures of oral hygiene or periodontal disease were not significantly different between cases and controls.

History of invasive procedures

Case participants had significantly fewer dental hygiene visits in the 12 weeks prior to enrollment than control participants (14.5% vs 36.1% p=0.002) (Appendix Table 4). There were no other statistically significant differences in the exposure of cases and controls to invasive dental procedures during this time period. Participants were also evaluated for exposure to 30 non-dental invasive procedures in the 12 weeks prior to enrollment (Appendix Table 5). There were no significant differences between case and control participants in these procedures except for upper gastrointestinal endoscopy and colonoscopy procedures, which occurred with significantly greater frequency in cases than controls (p=0.001 and p=0.004, respectively). For participants who had these procedures in the 12 weeks prior to enrollment, 8 of the 9 who had upper gastrointestinal endoscopy were cases and all 5 who had a colonoscopy were cases.

Trans thoracic and trans esophageal echocardiography

Evidence of mitral valve vegetation was identified in 34 cases (54.8%), the aortic valve in 32 (51.6%), and the tricuspid valve in 3 (4.8%) cases (Appendix Table 6). There was a greater frequency and more severe aortic regurgitation in cases compared to controls (p=0.021, <0.001 respectively). However, aortic stenosis (p=0.022) and hypertrophic cardiomyopathy (p=0.038) were identified less frequently in cases compared to controls. There was no difference in mitral valve prolapse between cases and controls.

Case blood culture microbiology

Blood culture results from IE cases were categorized according to the likelihood of bacterial origin from the mouth (Table 4). Common oral bacterial species, likely to have come from the oral cavity, were isolated from 27/62 (44%) of the blood cultures. Two cultures were streptococcal species but unidentifiable beyond the genus level. The remaining 33/62 (53%) bacteria were determined unlikely to represent oral species, although some have been identified in the oral cavity.[35,36] In a sub analysis of the primary outcome (Appendix Table 7), comparing cases with oral bacterial species only vs. all controls, cases persisted in having significantly higher mean calculus index (0.95, 0.55; difference = 0.40, p<0.001) and sum calculus index (22.3, 12.9; difference = 9.4, p<0.001) than controls.

DISCUSSION

In this study, IE cases had 53% higher mean dental calculus (primary outcome) and 26% more mean dental plaque than non-IE controls (Table 3). IE cases also had less frequent dentist or

dental hygienist office visits overall and fewer dental office visits in the 12 weeks preceding participation in this study (Table 2 and Appendix table 3). All of these data support and strengthen the long-standing hypothesis that poor oral health is associated with risk for IE[26] and the AHA guidance [9,10] that those at risk for IE from oral bacterial species can reduce their risk by maintaining optimal oral health. Thus, maintenance of oral hygiene may decrease the risk of IE among people at AHA moderate risk. This finding is particularly noteworthy, as there are currently no other recommended preventive therapies for IE in this group whose risk for IE and IE-related morbidity and mortality may be higher than generally appreciated.[37]

Modern molecular means of species identification have documented the wide range of anatomical sites where presumed oral bacterial species (*e.g.,* VGS) can be isolated. However, some bacterial species traditionally thought to be of non-oral origin such as *Enterococcus faecalis*, are often detected in necrotic tooth root canals[38]. This species was found in 10 of the 62 cases blood cultures (Table 4). Based on published studies of the oral microbiome, we were able to classify all but 2 of the 62 bacterial isolates as typically originating from an oral site (Table 4). or as "unlikely oral species" i.e., those primarily associated with other sites such as skin or the GI tract.[11,35,36,39] Our relatively high percentage (44%) of likely oral species from cases may be influenced by the exclusion of those with nosocomial, health-care associated, and intravenous drug related IE, which are more likely to be due to staphylococci. Nevertheless, our bacterial isolates data suggest a significant ongoing role for oral bacterial species as a cause for native valve IE.

Differences in cardiac status between cases and controls can mostly be attributed to sequelae of IE and study selection bias. For example, our finding of a higher prevalence of aortic regurgitation in cases is to be expected as a complication of IE (Appendix Table 6). More

frequent aortic stenosis and hypertrophic cardiomyopathy among controls are likely due to selection bias. Controls had been referred to cardiac referral centers for possible transcatheter valve procedures and they were receiving routine echocardiographic monitoring for such conditions. The lack of a difference in the prevalence of mitral valve prolapse between cases and controls is reassuring with respect to potential bias in the selection of cases and controls.

Cases were significantly more likely than controls to have had colonoscopy or endoscopy in the 12 weeks prior to study entry. However, we could infer a potential causal association with IE in only 1 of 5 colonoscopy cases, which was done prior to the hospital admission that led to the diagnosis of IE. The significantly higher prevalence of cigarette smoking history for cases (p=0.032) is of interest because smoking is strongly associated with poor oral hygiene and periodontal disease.[14]

There were several reasons for choosing to enroll only people having AHA-defined moderate risk for our cases and controls, for example: 1) If we had included high-risk controls, there would have been ethical concerns about the need to give them antibiotic prophylaxis prior to performing the invasive parts of the study oral examination; 2) the moderate risk group represents about 90% of all people known to be at risk of IE;[8] and 3) there is a general assumption that if oral hygiene is a risk factor in those at moderate risk then it is also likely to be a risk factor for those at high risk;[37]

There are limitations to this study. For example, given our methodology of examining cases and controls in different hospital locations, we could not blind the examiners as to whether participants were cases or controls. Furthermore, the four enrollment site hospitals are quaternary referral centers whose patients may be more complex than those seen in community hospitals. In

addition, the study was terminated due to funding limitations prior to enrolling the original estimated sample size. However, analysis of the available data indicated a highly significant association ($p<0.002$) for the primary outcome of dental calculus and a post-hoc power analysis revealed power of 0.80 or more for calculus, as well as a marginal, but statistically significant association ($p<0.04$) for the secondary outcome of dental plaque.

The 2000 Institute of Medicine report on Medically Necessary Dental Services, along with AHA recommendations, have long indicated the need to clarify the role of oral hygiene in the pathogenesis of IE.[2,10,40] Additionally, as is the case for the general public, some of those at risk of developing IE may have limited access to dental care for a variety of reasons, as well as a limited understanding of the importance of achieving and maintaining good oral hygiene. For physicians and dentists, there remains a lack of understanding of the relative risks from infrequent invasive dental procedures versus repeated bacteremia from routine daily activities (*e.g.,* toothbrushing) in those with poor oral hygiene, which adds to the challenge of IE prevention. Our data provide evidence that maintenance of oral hygiene may be an important factor in mitigating risk for IE.

CONCLUSIONS

These data provide evidence to support and strengthen current AHA guidance[9,10] that those at risk for IE can reduce potential sources of IE-related bacteremia by maintaining optimal oral health through regular professional dental care and oral hygiene procedures.

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Appendix Material:

Appendix Tables 1-7

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Figure Legends:

Figure 1. Anatomy of a lower molar tooth, showing healthy gingiva (left) and inflamed gingiva with early periodontal disease (right)

Figure 1. Relationship of a lower molar tooth, alveolar bone, gingival and periodontal tissues. The left side shows the anatomy of the healthy gingival sulcus, lined by non-keratinized and highly permeable epithelium. The right side shows periodontal disease, caused by a biofilm of dental plaque. Tissue inflammation, periodontal pockets containing plaque and calculus and loss of tooth-supporting bone are clinical hallmarks of periodontal disease. Inset: Higher-power view of the gingival tissues associated with periodontal pocket formation and associated plaque biofilm and dental calculus (mineralized dental plaque) accumulation. The gingivae have become inflamed and swollen with dilated blood vessels. The periodontal pocket is a chronic inflammatory lesion which contains inflammatory exudate and pathogenic bacteria and their products (e.g., enzymes, endotoxins). It is lined by highly permeable non-keratinized and ulcerated epithelium. Increased permeability and loss of the epithelial barrier allows for bacterial invasion into the underlying inflamed connective tissue with a resulting bacteremia.

Figure 2. Study Enrollment