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THE EFFECT OF USING MOUTHWASHES TO PREVENT BACTEREMIA DURING INITIAL THERAPY OF PERIODONTAL TREATMENT

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III. ABBREVIATIONS

AHA: American Heart association

BIO: Biotene

CHX: Chlorhexidine

GI: Gingival Index

IE: Infective endocarditis

PCR: Polymerase Chain Reaction

PI: Plaque Index

PP: Pour-Plate

PPD: Probing Pocket Depth

Rp: Root planing

SBC: Signal Blood Culture

Sc: Scaling

Sc/Rp: Scaling and root planing

US: Ultrasonic Scaling

ml: milliliter

°C: Degree Centigrade

%: Percentage

<: Less than

>: More than

cfu: Colony forming unit

et al.: el alibi

g: Gram

hr: Hour

im: Intra -muscular

iv: Intra-venous

kg: Kilogram

mg: Milligram

min: Minute

mm: Millimeter

p: Probability

s: second

sp: Species

1.1. SUMMARY

Bacteremia means the presence of viable bacteria in the circulating blood. Dental procedures including periodontal therapy may induce bacteremia with the potential to produce distant infections in high-risk patients. The aim of this study is to evaluate the effect of Biotene mouthwash on the incidence of bacteremia during initial periodontal therapy and to compare the efficacies of Biotene and chlorhexidine to find out if Biotene is as effective as chlorhexidine.

This study included 30 chronic gingivitis patients with no medical history and antibiotic therapy within the previous 3 months. They were assigned to 3 groups; each group comprised 10 patients, Biotene group, 0.2% chlorhexidine gluconate group, and normal saline as a control group. Blood samples were taken at four different time points during ultrasonic scaling (US). Then, they were cultured aerobically and anaerobically by using Signal Blood Culture System and pour-plate methods.

Bacteremia was detected in 4 patients of Biotene group (40%), in 3 patients of chlorhexidine group (30%), and in 5 patients of control group (50%). Within the limit of this study, Biotene is as effective as chlorhexidine in reducing the incidence of bacteremia since pre-procedural rinsing with Biotene and 0.2% chlorhexidine resulted in the same reduction in the incidence of bacteremia associated with US. On the other hand, they were both effective in reducing bacteremia and better than control group.

Key words: Bacteremia, infective endocarditis, prophylaxis, chlorhexidine, Biotene.

BAŞLANGIÇ PERIODONTAL TEDAVI SIRASINDA OLUŞACAK BAKTERIYEMIYI ÖNLEMEK İÇIN AĞIZ GARGARALARININ KULLANIMININ ETKISI

1.2. ÖZET

Bakteriyemi kan dolaşımında bakterilerin varlığı anlamına gelir. Periodontal tedaviyi içeren dental işlemler yüksek risk grubundaki hastalarda ciddi enfeksiyonlar oluşturma potansiyeline sahiptir. Bu çalışmanın amacı başlangıç periodontal tedavi esnasında oluşan bakteriyeminin önlenmesinde Biotene ağız gargarasının etkinliğini değerlendirmek ve klorheksidin ile karşılaştırmaktır.

Bu çalışmaya son üç ay içinde antibiyotik kullanmamış ve herhangi bir sistemik hastalığı olmayan 30 hasta dahil edildi. Çalışma, her bir grup 10 kişiden oluşmak kaydıyla 3 grup üzerinde yapıldı. Bunlar Biotene, %0.2 klorheksidin ve kontrol olarak ta serum fizyolojik grubu idi. Tüm deneklerden ultrasonik cihaz ile yapılan başlangıç periodontal tedavi esnasında 4 farklı zamanda kan örnekleri alındı. Sonra bu örnekler *pour-plate* methodu ve Signal *Blood Culture System* kullanılarak aerobik ve anaerobik olarak kültüre edildi.

Biotene grubuna ait 4 hastada (%40), klorheksidin grubuna ait 3 hastada (%30) ve kontrol grubuna ait 5 hastada (%50) bakteriyemi tespit edildi. Bu çalışmanın sınırları dahilinde, bakteriyeminin önlenmesinde Biotene, klorheksidin kadar etkili bulunmuştur. Diğer yandan hem Biotene hem klorhexidin bakteriyeminin azaltılmasında kontrol grubundan daha etkilidir.

Anahtar kelimeler: Bakteriyemi, enfektif endokardit, profilaksi, klorheksidin, Biotene.

2. INTRODUCTION

It is well known that microbial dental plaque is the major causative factor of periodontal diseases (2). Therefore, the principal objective of periodontal therapy is to eliminate the pathological bacterial presence and to prevent or minimize the recolonization of the sub- and supra-gingival area by pathogenic microflora. This objective can be achieved by the initial periodontal therapy (9, 115). However, these procedures may damage the gingival tissues resulting in invasion of the bloodstream by oral microorganisms. The presence of viable bacteria in the circulating blood is known as bacteremia. This phenomenon usually considered of little significance except in patients with rheumatic or congenital heart disease. In such patients, circulating bacteria may reach to the vulnerable endocardium and cause infective endocarditis (IE). In addition to heart disease patients, synthetic vascular graft, systemic pulmonary shunts, and prosthetic joints patients are also considered as high-risk patients (26, 89, 110). Recently, some periodontal pathogens including *Porphyromonas gingivalis, Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans,* have considerable attention because they can be detected in a significant proportion of atherosclerotic plaques and abdominal aortic aneurysms. The pathogenic significance of their presence is not known yet (51).

Odontogenic bacteremia is proved to occur with oral hygiene procedures and the dental procedures increase the probability of occurrence of bacteremia. In 1980, the American Heart Association (AHA) recommended prophylactic antibiotic regimens for patients who are at risk of developing IE resulting from transient bacteremia associated with invasive dental procedures (10). While these regimens are largely successful, IE following dental procedures could not been completely prevented (114). On the other hand, antibiotic prophylaxis cannot be prescribed on daily basis of all dental treatment procedures due to its known side effects. Therefore, other methods must be introduced to decrease the occurrence of bacteremia after dental procedures (10, 27, 114). The use of antimicrobial mouthwashes may effectively lower the number of bacteria in oral cavity, hopefully, lessening the chance of bacteremia during dental treatment (17, 23, 27, 117). In 1986, in an effort to reduce the incidence of failed prophylactic antibiotic regimens to prevent bacteremia, AHA recommended antiseptic mouthwashes prior to

dental procedures in order to reduce the incidence and severity of bacteremia (114). One of the most effective mouthwashes among these is chlorhexidine (CHX) applied via gentle oral rinsing 3-5 minutes (min) before the procedures. However, its frequent use is not recommended as this may result in formation of new forms of resistant bacteria such as resistant S*treptococci, enteric gram-negative rods, Pseudomonas* and *Enterococci*. In addition, it has other side effects including desquamation of gingiva, inflammation of salivary gland ducts, changes in taste, and staining of teeth and porcelain (40).

Biotene (BIO) mouthwash is an alcohol free strong antimicrobial system that contains the same exact enzymes naturally produced by the mouth. These enzymes are lysozyme, lactoferrin, glucose oxidase and lactoperoxidase. They boost the defense system normally found in the normal saliva (55, 68) and exert a wide antimicrobial activity against a number of bacterial, viral and fungal pathogens (13, 41, 43, 49, 55, 65, 68, 78, 105, 108).

The clinical and microbiological advantages of using antimicrobial agents as coolants during ultrasonic scaling (US) are not well documented. In the previous studies of bacteremia induced by US, antimicrobial agents were used for rinsing and sub-gingival irrigation only (59, 79, 117). In the presented study, antiseptic mouthwashes were used not only as mouthrinse but also as coolant during US to prevent bacteremia; and to our knowledge, this is a new method that has not been performed in bacteremia studies in the literature.

The aims of this study are to evaluate the effect of using BIO mouthwash on the incidence of bacteremia during initial periodontal therapy; in addition, we wanted to compare the efficacies of BIO and CHX on the incidence of bacteremia in order to find out if BIO is as effective as CHX; and the last, we introduced a new method to increase the efficacy of antiseptic mouthwashes on the incidence of bacteremia associated with US by using the antibacterial mouthwashes as a coolant in addition to their usage as a mouthwash.

3. LITERATURE REVIEW

3.1. Oral Microflora

The mucous membrane of the mouth and pharynx are often sterile at birth but might be contaminated after passage through the birth canal. Within 4-12 hours (hr) after birth, *Streptococci* become established as the most prominent members of the resident flora and remain so for life. Other microorganisms such as aerobic and anaerobic *Staphylococci,* gram negative *Diplococci (Neisseriae, Moraxella cataralis), Diphtheroids,* and occasional *Lactobacilli* are added later. In the pharynx, the prominent organisms are non-hemolytic and alpha-hemolytic *Streptococci* and *Neisseriae* species (sp). *Staphylococci, Haemophilus, Pneumococci, Mycoplasma,* and *Prevotella* are also encountered (64).

After the eruption of teeth, dental plaque and complex microbial communities start to form on virtually all surfaces of the teeth exposed to the bacteria-laden fluids of the mouth (123). These microbial communities might be formed on tooth surfaces, both supragingivally and subgingivally (Picture 1a, b), and may adhere to prosthetic and orthodontic appliances. They are of considerable clinical importance because they are the primary etiologic agents in the development of periodontal diseases. Table 1 shows the approximate proportional distribution of bacteria on various oral surfaces and in saliva.

	
Picture 1a	**Picture 1b**

Picture 1a, b: Microbial dental plaque

Table 1. Approximate proportional distribution of bacteria on various oral surfaces and in saliva (31).

Bacteria	Gingival Crevice	Coronal Plaque	Tongue Dorsum	Buccal Mucosa	Saliva
Streptococcus salivarius	<0.5%	<0.5%	20%	11%	20%
Streptococcus mitis	8%	15%	8%	69%	20%
Streptococcus sanguis	8%	15%	4%	11%	8%
Streptococcus mutans	?	0-50%	<1%	<1%	<1%
Enterococci	0-10%	<0.1%	<0.01%	<0.1%	<0.1%
Gram-positive *filaments*	35%	42%	20%	?	15%
Lactobacilli	<1%	<0.005%	<0.1%	<0.1%	<1%
Veillonella sp	10%	2%	12%	1%	10%
Neisseria sp.	<0.5%	<0.5%	<o.5%	0.5%	<1%
Bacteroides oralis	5%	5%	4%	?	?
Bacteroides melaninogenicus	6%	<1%	<1%	<1%	<1%
Vibrio sputorum	5%	1%	<0.5%	0.5%	?
Spirochetes	2%	<0.1%	<0.1%	<0.1%	<0.1%
Fusobacterium sp	3%	4%	1%	?	<1%

At periodontally healthy sites, the plaque samples taken from gingival sulcus contain low microbial load. Although extensive variations exist across studies, there is general agreement that the cultivable bacteria at healthy sites are mostly gram-positive and belong to the *Streptococcus* and *Actinomyces* genera. Approximately 75% to 80% of the recoverable microflora is gram-positive with most of the remainder belonging to gram-negative sp of the *Veillonella* and *Fusobacterium* genera. It is not surprising that these bacteria are associated with healthy sites because they are prominent early colonizers of tooth surfaces and gingival crevices. In naturally occurring gingivitis, although the microbial load at diseased sites is greater than the associated load at the healthy sites,

the dominant bacteria are gram-positive sp. In addition to the increased microbial load at sites with gingivitis, there is a general shift toward increasing proportions of gram-negative bacteria and increase in the number of motile bacteria including cultivable and uncultivable *Treponemas*. The microflora of sites displaying the clinical features of chronic periodontitis exhibits a spectrum of bacterial sp similar to that found in naturally occurring gingivitis. However, the proportions of the individual bacteria usually vary between the two diseases. In general, sites with chronic periodontitis are populated with greater proportions of gram-negative organisms and motile bacteria. Certain gram-negative bacteria with pronounced virulence properties like *Porphyromonas gingivalis* and *Tannerella forsythensis (Bacteroides forsythus)* have been strongly implicated as etiologic agents. Coaggregating bacteria such as *Actinomyces naeslundii*, *S. sanguis*, and *F. nucleatum* are among the most numerous bacteria isolated from dental plaque irrespective of disease status. In aggressive periodontitis patients, the microflora of subgingival biofilms is similar to that of patients with chronic periodontitis but this kind of periodontal disease is characterized by sever attachment loss over a short period of time. On a percentage basis, the most numerous isolates are several sp from the genera *Eubacterium, A. naeslundii, F. nucleatum, C. rectus,* and *Veillonella parvula*. In some populations, *A. actinomycetemcomitans* play a causative role. However, some populations of patients with aggressive periodontitis do not harbor *A. actinomycetemcomitans*; in some others *P. gingivalis* may be etiologically more important (60).

Dissemination of oral microorganisms into the bloodstream during initial therapy of periodontal treatment is common resulting in bacteremia (20, 25, 86, 103). Oral microorganisms from the infected site may reach the heart less than 1 min after an oral procedure (47). These microorganisms may lead to cardiovascular diseases (39). *S. viridans* is the most widely isolated bacteria in blood cultures, either by themselves or together with other germs (8). They cause the vast majority of infective endocarditis (IE). The propensity of these organisms to elicit IE is due to at least three factors: 1) their main habitat on mucous membranes, which allows for frequent entry into the blood, 2) an exceptional ability to adhere to damaged cardiac tissues, and 3) an ability to survive and thrive in the nonbacterial thrombotic vegetation of the cardiac tissues (73).

3.2. Initial Therapy in Periodontal Treatment

Initial therapy is the first step in the sequence of periodontal treatment procedures. Its primary objective is to remove microbial dental plaque to alter or eliminate the microbial etiology and to remove the contributing factors of gingival and periodontal diseases. It is referred to by a number of names including phase I therapy, non-surgical periodontal therapy, cause related therapy, and the etiotropic phase of therapy. The reduction and elimination of etiologic and contributing factors is achieved by complete removal of calculus, correction of defective restorations, treatment of carious lesions, and comprehensive daily plaque control regimens (75).

Initial therapy has many goals that go beyond the control of inflammation and pocket reduction by mechanical means. The American Academy of Periodontology has included the following aspects in the parameters of care for this phase (2):

1. Evaluation and alteration of patient systemic risk factors
2. Plaque control performed by the patient
3. Removal of microbial plaque and calculus from the surface of the teeth
4. Appropriate use of antimicrobial agents and devices including necessary plaque sampling and antibiotic sensitivity testing
5. Control or elimination of contributing local factors including the following:
    A. Treatment of poorly fitting restorations
    B. Correction of poorly fitting prosthetic devices
    C. Restoration of carious lesions
    D. Odontoplasty
    E. Tooth movement
    F. Treatment of food impaction areas
    G. Treatment of occlusal trauma
    H. Extraction of hopeless teeth

Based on the knowledge that microbial dental plaque harbors the primary pathogens of gingival inflammation, effective plaque control is the key objective of every therapeutic periodontal procedure. Plaque control is the best accomplished if tooth surfaces are free of rough deposits which can be obtained by scaling (Sc) and root planing (Rp).

3.2.1. Scaling and Root Planing

Sc is the process by which plaque and calculus are removed from both supra- and sub-gingival tooth surfaces. Rp is the process by which residual embedded calculus and portions of cementum are removed from the roots to produce a smooth, hard, and clean surface. Sc/Rp are not separated procedures. They have the same principles and can be done by either hand instruments or ultrasonic instruments. The difference is only a matter of degree (74). The primary objective of Sc/Rp is to restore gingival health by removing the elements that provoke gingival inflammation (plaque, calculus, and endotoxin) from the tooth surfaces. They can reduce the numbers of subgingival microorganisms and changes the composition of subgingival plaque from one with high numbers of gram-negative anaerobes to one dominated by gram-positive facultative bacteria that are compatible with health. In addition, Sc/Rp can cause reduction of spirochetes, motile rods, and putative pathogens such as *A. actinomycetemcomitans, P. gingivalis,* and *P. intermedia,* and produce an increase in the coccoid cells. These changes in the microbiota are accompanied by a reduction or elimination in the clinical signs and symptoms of inflammation (74). During the performation of these procedures, damage to the gingival tissues may occur resulting in a serious phenomenon known as bacteremia.

3.3. Bacteremia

Bacteremia means an invasion of the bloodstream by bacteria or the presence of viable bacteria in the circulating blood. Dissemination of oral microorganisms into the bloodstream is common during and after dental procedures. On the other hand, bacteremia usually considered of little significance because the microorganisms that gain entrance to the blood circulation are usually eliminated by reticuloendothelial system. However, in favorable conditions, circulating bacteria may settle at vulnerable sites and start to multiply. These regions might be cardiac valves, synthetic joints, or synthetic vascular grafts. Some gram-positive and gram-negative bacteria have the ability to produce diffusible proteins or exotoxins which include cytolytic enzymes and dimeric toxins. These exotoxins have specific pharmacological actions and are

considered the most powerful and dangerous poisons known. In addition to exotoxins, bacterial endotoxins are involved in the process of bacteremia. They are part of the outer membranes released after bacterial cell death. The endotoxin is compositionally a lipopolysaccharide that when introduced into the host gives rise to a large number of pathological manifestations. It may promote atherosclerosis, and affect many hematologic and immunologic events including blood coagulation, the function of platelets, and the prostaglandin synthesis. Such functions are important in thrombus formation which may lead to cerebral and myocardial infarction. Soluble antigen may enter the bloodstream, react with circulating specific antibody and form a macromolecular complex. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the sites of deposition (47). In patients with heart disease or synthetic valve implants, IE may develop which is a serious and often fatal systemic condition (10).

3.3.1. Infective Endocarditis

Intact cardiac endothelium is a poor stimulator of blood coagulation and resistant to microbial colonization. However, once this endothelium, usually in the region of a cardiac valve, is damaged by turbulent blood flow, direct trauma or age-or disease-dependent degeneration, platelets and fibrin may deposit to form nonbacterial thrombotic vegetation (26). If blood borne bacteria adhere to the surface of the nonbacterial thrombotic vegetation, additional layers of fibrin and platelets may cover these bacteria to isolate them from the host defenses and allow further growth of the organisms causing infected vegetation (26). The infection of the cardiac tissue or its related structures notably valves and their apparatus is known as IE (50, 110). This is a well known complication of congenital and acquired heart disease and usually develops in individuals with cardiac defects who develop bacteremia with organisms likely to cause endocarditis (10).

3.3.1.1. The Infective Microorganism

Streptococcus strains cause the vast majority of IE (73). In the era before antibiotics, more than 80% of all endocarditis cases were caused by *Streptococci* (the v*iridans* group, Enterococci, beta-hemolytic, and *S. pneumoniae*) (72). In 1970s, the incidence of streptococcal endocarditis began to decline to 50-60%. Of the entire *Streptococcus* sp, *S. viridans* including *S. sanguis*, *S. mitis, S. mutans*, *S. anginosus,* and *S. salivarius* are present in 75% of the cases (8, 73). In addition to *Streptococcus*, other microorganisms including *Staphylococcus, Enterococci, Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*, *Neisseria gonorrhoeae*, *Pseudomonas, Salmonella, Streptobacillus, Serratia marcescens, Bacteroides, Brusella, Mycobacterium, Legionella, Candida*, *Aspergillus*, *Spirillum minor, Coxiella burneti and Chlamidia* are involved in the pathology of IE (8).

3.3.1.2. Infective Endocarditis of Oral Origin

It has long been a prevalent view that dental procedures performed without appropriate precautions on patients with predisposing conditions such as rheumatic heart disease, congenital cardiac malformations, previous cardiac surgery, and the use of prosthetic heart valve, may be intimately associated with the development of IE. When the endocardium becomes infected with microorganisms that have entered the circulation (via dental procedures, through the gingiva, and/or the oral mucosa), the progressive destruction of the endocardium may lead to anemia, toxemia, and ultimately cardiac failure which is the most common cause of death in these patients. Such a concept is based on three facts (87):

1- There is a close similarity in the majority of cases between the etiological agent responsible for the disease and the organisms found in the mouth in pulps and periapical areas of teeth.
2- Symptoms of the disease have been observed in some instances shortly after extraction of teeth.
3- Many studies indicate that transient bacteremias occur quite frequently following extraction of teeth.

The first suggestion of a link between IE and oral bacteremia was raised in 1909 (42). In that year, Horder (42) noted the association between *S. viridans* present in the mouth and upper respiratory tract and IE in patients with previous heart disease. Since then, there have been multitudes of studies and experiments that have provided a great deal of circumstantial evidence to support this link (66, 106, 111). However, these studies do not conclusively show that dental treatment may induce a bacteremia that is directly responsible for the development of IE in humans. Strom et al. (100) quantitated the risk for endocarditis from dental treatment and cardiac abnormalities. It was a population-based-case-control study conducted in 54 hospitals in Philadelphia area. In this study, persons with community-acquired IE not associated with intravenous drug use were compared with community residents matched by age, sex, and neighborhood of residence. IE patients more often had a history of mitral valve prolapse, congenital heart disease, cardiac valve surgery, rheumatic fever, and heart murmur without other known cardiac abnormalities. Information on demographic characteristics, host risk factors, and dental treatment was obtained from structured telephone interviews, dental records, and medical records. Few participants received antibiotic prophylaxis. They found that during the preceding 3 months, dental treatment was no more frequent among case-patients than controls. Of 273 patients, 104 (38%) known of previous cardiac lesion compared with 17 controls (6%). Among patients with known cardiac lesion, the effect of antibiotic prophylaxis was significantly ($p=0.03$) less than among the controls. They concluded that dental treatment does not seem to be a risk factor for IE even in patients with valvular abnormalities. Few cases of IE would be preventable with antibiotic prophylaxis even with 100% effectiveness assumed. They defined the risks of IE associated with various dental procedures (101). It was a population-based-case-control study conducted in 54 Philadelphia, Pa-area hospitals from 1988 to 1990. Community-acquired IE cases unassociated with intravenous drug use were compared with matched community residents. Subjects were interviewed for risk factors. Edentulous patients had a lower risk of IE form dental flora than patients who had teeth but did not floss. Daily flossing was associated with a borderline decreased IE risk. They concluded that IE patients differ from people without IE with regard to certain important risk factors not regarding recent procedures. Mostaghim and Millard (66) examined the medical records of 60 patients with bacterial endocarditis at the Hospital of Michigan University

from 1962 to 1972. Oral conditions and dental procedures were related to the onset of bacterial endocarditis in 14% of these patients. The dental procedures included polishing, tooth capping, orthodontic treatment, root canal therapy, and extractions. In addition, treatment was given for pericoronitis and dental abscess. The mortality rate for these patients during the 10 years of study was 33%. Although the risks of bacterial endocarditis in patients with a history of rheumatic fever or congenital heart disease were small, patients with a previous episode of bacterial endocarditis or patients with prosthetic heart valves were very susceptible to bacterial endocarditis.

3.3.2. Systemic Pulmonary Shunts

Normally, pulmonary blood flow and systemic blood flow are equal. With an abnormal communication between intracardiac chambers or greater vessels, blood flow is shunted either from the systemic circulation to the pulmonary circulation (left-to-right shunt), from the pulmonary circulation to the systemic circulation (right-to-left shunt), or in both directions (bidirectional shunt) (19). Systemic pulmonary shunt is a major strategy for the palliation of cyanotic congenital heart disease lesions despite the associated morbidity and mortality of surgically created connections between the aorta and a pulmonary artery (52). This procedure is palliative aiming to increase the blood supply to the lungs and the arterial oxygen saturation. Congenital cardiac lesions that involve high-velocity jets of blood flow and/or foreign material are associated with the highest risk for development of IE. Thus, patients with complex cardiac anatomy who had undergone palliative shunt and conduit procedures were found to be the largest group at risk (26). American Heart Association (AHA) recommends antibiotic prophylaxis prior to dental treatment procedures for patients with such morphologic alterations (17).

3.3.3. Synthetic Vascular Graft

Conditions such as hypertension, diabetes, and especially atherosclerosis may lead to peripheral artery occlusion or development of an aneurysm. Under these circumstances, prosthetic vascular graft materials such as Dacron and polytetrafluoroethylene are sutured into vascular walls to restore circulation or prevent aneurysm rupture (11).

The risk of graft infections from transient oral bacteremia is unknown. But, any presumed risk diminishes as the graft incorporates into the host tissue. Pseudointima composed of connective tissue and fibrin begins to form on the inner surface of the graft. True endothelium does form but rarely extends more than 10 mm beyond the anastomosis. This process may take three to six months and does not preclude the possibility of late graft infection (110). The most common microorganisms isolated from infected vascular graft were *Staphylococcus, E. coli, Klebsielle, Pseudomonas,* and *Streptococci* (45).

Most authors agree that antibiotic prophylaxis is indicated for new grafts of less than six months (110) but only Lindeman and Henson (56) recommended antibiotic prophylaxis prior to dental procedures of any synthetic vascular graft. Physician consultation to confirm the type, location, and size of the graft along with reinforcement of strict oral homecare would seem prudent.

3.3.4. Prosthetic Joints

Prosthetic replacement of large joints such as hip, knee, elbow and shoulder is an increasingly common and highly successful orthopedic surgical procedure. Bacteremia can cause hematogenous seeding of total joint implants which is a devastating complication that can lead to loss of the prosthetic joint and serious morbidity for the patient (89). It appears that the most critical period is up to two years after joint placement (36). Patients who are about to have a total joint arthroplasty should be in good dental health prior to surgery and should be encouraged to seek professional dental care if necessary. Patients who already have had a total joint arthroplasty should perform effective daily oral hygiene procedures to establish and maintain good oral health (73). The possibility of prosthetic joint infection from odontogenic bacteremia has encouraged some dentists and orthopedic surgeons to recommend antibiotic prophylaxis for all patients with prosthetic joint replacement when undergoing dental treatment. However, reviews of the literature have concluded that there is minimal evidence of hematogenous infection of prosthetic joints by oral organisms (113).

The most common microorganisms associated with prosthetic joint infections are the *Staphylococci*. *S. aureus* was the most common isolate followed by the gram-negative rods *Escherichia coli* and *Pseudomonas* sp, *S. epidermidis*, and *Enterococcus* sp (44). Early infections (defined as those occurring in the first postoperative year) were most commonly caused by *S. epidermidis, S. aureus,* and *Streptococcus* sp. Late postoperative infections were also primarily caused by S*taphylococci* but gram-negative rods were commonly recovered as well (21). Despite the low risk of blood-borne prosthetic joint infection of artificial joints by oral organisms, some medical and dental practitioners prefer antibiotic cover in any circumstance likely to produce bacteremia of oral organisms. Patients at potentially increased risk are listed in Table 2.

Table 2. Patients with following medical conditions are at potentially risk of prosthetic joint replacement infection (113).

Inflammatory arthropathies and rheumatoid arthritis
Immunocompromised and immunosuppressed
Diabetes mellitus
Steroid replacement therapy
Malnourishment
Hemophilia
Previously infected prosthetic joints
Prosthetic joint replacement surgery within the past 2 years

3.3.5. Oral Microflora and Bacteremia

The human oral cavity is colonized by more than 700 bacterial sp, of which more than 50% have not been cultivated yet (1). They are considered nonpathogenic as long as they are confined within the mouth. Dissolution of the continuity of the mucous membrane or disruption of the capillaries in the gingival tissues may occur during daily oral activities such as chewing gum and oral hygiene procedures, dental procedures and extensive surgery (20). These oral microorganisms may seed into the blood stream resulting in bacteremia and harmful complications (20, 24, 25, 80, 86, 103). This type of

bacteremia may be only transient lasting for 30 second (s) to 30 min (22). It is insignificant in healthy patients due to the efficient clearance by the host's immune system since the microorganisms that gain entrance to the blood are usually eliminated by reticuloendothelial system within a few minutes. However, bacteremia may be a potential danger in medically compromised patients whose immune system is affected because of drug use, damaged organs, congenital and rheumatic heart disease, prosthetic valve replacement, heart murmurs, aortic valve disease, diabetes, and acquired immune deficiency syndrome (AIDS). In such patients, bacteremia may be a potential danger leading most commonly to IE (20, 30, 57, 59, 70, 96, 125). Therefore, oral microflora is of a big significance as it can be a source of bacteremia (4, 15, 20, 59, 71).

3.3.6. Microbiology of Odontogenic Bacteremia

The microorganisms that are usually associated with bacteremia and obtained from blood samples in different oral procedures are *Streptococcus* sp *(S. intermedius, S mitior, S. sanguis, S. salivarius,* and *S. mutans).* In addition, *Actinomysis, Prevotella melaninogenica, P. intermedia/nigrescens, Veillonella, Peptostreptococcus, Haemophylus, Fusobacterium, Capnocytophaga*, *Enterococcus, Corynebacterium, Porphyromonas*, *Bacteroides*, *Lactobacillus, Neisseria, Staphylococcus, Micrococcus, Propionibacterium,* unidentified aerobic gram-positive bacilli, unidentified aerobic gram-negative bacilli and unidentified anaerobic gram-negative bacilli could be included in other responsible microorganisms for odontogenic bacteremia (37, 103).

3.3.7. Bacteremia-Producing Dental Procedures

General dental practitioners often express concerns as to what dental procedures produce bacteremia and who is at risk from such bacteremia. In the 1930s, it had become clear that various dental procedures might induce bacteremia (72). Poor oral hygiene, especially periodontal status or periapical infections may produce bacteremia even in the absence of dental procedures (30). Gingival inflammation correlates positively with the prevalence and magnitude of bacteremia. However, the bleeding is a poor predictor of odontogenic bacteremia (30, 92, 93). Bacteremia is induced by a wide

variety of procedures and manipulations including normal oral functions, oral hygiene procedures, and dental procedures such as probing, Sc/Rp, periodontal surgery, endodontic therapy, extraction, biopsy, and extensive surgeries (20, 24, 37, 48, 62, 79, 83, 85, 93, 95, 103).

The incidence and magnitude of bacteremia of oral origin are directly proportional to the intensity of performed procedure and the degree of oral inflammation (20, 30, 71) and may be related to the nature and the volume of the oral microorganisms. The prevalence of such bacteremia and the associated procedures are shown in Table 3 (92).

Table 3. Incidence of bacteremias arising after various types of dental procedures and oral activity (92)

Procedure	**Prevalence of Bacteremia**
Extraction	
Single	51%
Multiple	68-100%
Periodontal surgery	
Flap procedure	36-88%
Gingivectomy	83%
Scaling and root planing	8-80%
Periodontal prophylaxis	0-40%
Endodontics	
Intracanal instrumentation	0-31%
Extracanal instrumentation	0-54%
Endodontic surgery	
Flap reflection	83%
Periodontal curettage	33%
Tooth brushing	0-26%
Dental flossing	20-58%
Interproximal cleaning with toothpicks	20-40%
Irrigation devices	7-50%
Chewing	17-51%

3.3.8. Bacteremia in the Dental Literature

Bacteremia associated with different dental procedures has been investigated by variety of studies. These studies revealed different results because of the used technique, site of blood withdrawal, timing of the blood sampling, blood volume, the degree of periodontal inflammation, quantity and composition of the gingival flora, and performed dental treatment. On the other hand, without any professional dental treatment, patient's daily activities including chewing gum and tooth brushing may induce odontogenic bacteremia. In 1979, Silver et al. (95) investigated the incidence of bacteremia after toothbrushing. Thirty-six subjects with no evidence of clinical gingival inflammation underwent standardized toothbrushing procedure. Brushing was done for 2 min. Blood samples obtained from antecubital vein during the last 30 s of brushing were cultured under aerobic and anaerobic conditions. They found that three subjects had detectable bacteremia after the brushing. *Propionibacterium* sp were isolated from two of the subjects while *Actinomyces* sp and *Streptococcus* sp were isolated from the other subject. They concluded that high-risk patients should have appropriate antibiotic cover when undergoing dental treatment.

In a most recent study, Forner et al. (30) determined the incidence, magnitude, duration, and nature of bacteremia after chewing, tooth brushing, and Sc. Sixty systemically healthy individuals were included in the study. They were categorized into three groups; periodontitis, gingivitis, and healthy periodontium. The three experimental procedures were: (1) chewing on three pieces of chewing gum base performed for 10 minutes (min), (2) tooth brushing performed for 2 min, and (3) full mouth Sc by a combination of hand instruments and air scaler. Blood samples of 9 ml of each were collected at baseline, 0.5 min, 10 min, and 30 min after each procedure and were examined for bacteremia by the lysis filtration method. None of the 60 subjects were detectably bacteremic before the three experimental procedures. Following chewing four (20%) of the periodontitis patients were bacteremic whereas none of the periodontally healthy individuals or gingivitis patients showed evidence of bacteremia. None of the periodontally healthy individuals or gingivitis group was bacteremic after tooth brushing. In periodontitis group, one (5%) of the patients was bacteremic immediately after tooth brushing and another patient was bacteremic after 30 min. Bacteremia after

Sc occurred in two (10%) of the healthy participants, in four (20%) of the gingivitis patients, and in 15 (75%) of the periodontitis patients. Among the 29 bacteremic episodes after termination of chewing, tooth brushing, or Sc, nine remained uncleared after 10 min. Seven of the nine episodes occurred after Sc while the remaining two occurred after tooth brushing. After 30 min, bacteremia was detectable in four individuals. Among these four episodes, one occurred after chewing, one after tooth brushing, and two after Sc. The isolated bacterial sp were *Streptococcus*, *Enterococcus*, *Actinomyces*, *Lactobacillus*, *Porphyromonas*, *Prevotella*, *Fusobacterium*, and one isolate of *Candida*. The most predominant isolates were *Streptococcus* sp. They concluded that patients with periodontitis as compared with healthy individuals and gingivitis patients are at increased risk of experiencing bacteremia in association with Sc. Moreover, their study suggests an increased risk of bacteremia in periodontitis patients after chewing and tooth brushing although this was not statistically significant.

Only a simple periodontal probing might induce bacteremia (18). Daly et al. (18) investigated the occurrence of bacteremia caused by full mouth periodontal probing. Forty patients, 20 with chronic gingivitis (10 males, 10 females) and 20 with adult periodontitis (10 males, 10 females) were included. 20 ml venous blood were obtained prior to and immediately following periodontal probing from each patient and inoculated into aerobic and anaerobic blood culture bottles. Bottles that signaled positive results were subcultured and isolates identified to genus level. Bacteremia was detected in 2 (10%) of the gingivitis patients and 8 (40%) of the periodontitis patients. *Streptococcus* sp were the most common isolates in both groups. Bleeding on probing and mean probing pocket depth (PPD) per tooth were significantly associated with bacteremia. No significant correlation was found between bacteremia and age, number of teeth probed, smoking status, plaque accumulation. They suggested that patients with untreated adult periodontitis are at greater risk of bacteremia due to periodontal probing than patients with chronic gingivitis. For this reason, in the treatment of medically compromised patients, they concluded that radiographic assessment prior to periodontal probing would be advisable to identify those with periodontitis so that appropriate antibiotic prophylaxis could be provided prior to periodontal probing.

Kinane et al. (48) evaluated the incidence of bacteremia in chronic periodontitis patients following probing, toothbrushing, and US. Thirty patients with untreated periodontal disease attended this study. Blood samples were obtained before and after the procedures. They were analyzed for bacteremia using conventional microbiological culture and polymerase chain reaction (PCR) using universal bacterial primers that target a vast majority of bacteria. Using culture methods, the incidence of bacteremia was as follows: US (13%), periodontal probing (20%) and toothbrushing (3%). PCR analysis revealed bacteremia incidences following US (23%), periodontal probing (16%) and toothbrushing (13%). They concluded that bacteremia did arise following various clinical periodontal manipulations (13 - 20%) as well as following toothbrushing. They added that the frequency of bacteremia detection was lower than that quoted by previous workers. They explained those results by the fact that patients with adult periodontitis might present a unique patient base whose immune systems were highly primed to cope with periodontal bacteria so that when a bacteremia was induced, it was quickly cleared by the patient's reticuloendothelial system.

Baltch et al. (4) studied the rate, type, and magnitude of bacteremia following US with and without the penicillin prophylaxis. Fifty-six moderate to severe periodontitis patients were included in the study. They were divided into 2 groups: (1) twenty-eight valvular heart disease patients received penicillin (US started within 15 to 30 min following completion of infusion). (2) twenty-eight patients without valvular heart disease received no penicillin. Dental cleaning procedure included US of soft and hard deposits. Blood samples were taken before, 5 min, and 10 min following completion of US. Bacteremia was detected in 61 % of the patients without penicillin prophylaxis at 5 minutes following the procedure. Significantly, less occurrence of bacteremia was detected in patients receiving penicillin prophylaxis (10%). However, the recovery of *Streptococci* was not significantly different in the two groups in terms of colony forming unit per milliliter of blood (cfu/ml). Of the 71 total bacterial isolates, 53 (74.6%) were anaerobes and 18 (25.4%) were aerobes. They indicated that parenteral penicillin prophylaxis for dental cleaning, significantly, decreased detectable bacteremia rates.

Odontogenic bacteremia is well documented following dental extraction and various dental surgical procedures. Rajasuo et al. (80) investigated bacteremia caused by surgical extraction of partially erupted mandibular third molars. From 16 young adults, bacterial samples were taken from the third molar peri-coronal pocket and post-operatively from the extraction socket, and blood samples were drawn from the antecubital vein up to 30 min after surgery. 88% of the subjects had detectable bacteremia (50% 1 min after the incision, 44% immediately after extraction). The respective percentages at 10, 15, and 30 min were 44%, 25%, and 13%. Blood cultures contained 31 sp (74% anaerobes) with 3.9 ± 2.6 sp isolated per subject. Most prevalent were the anaerobes including *Prevotella, Eubacterium, and Peptostreptococcus* sp, in addition, the aerobes including *S. viridans* and *S. milleri* groups. Any sp found in the blood was also isolated from the mouth, 93% from the peri-coronal pockets and 43% from the extraction sockets. They concluded that the surgical dental extraction clearly causes bacteremia of the high frequency and lasting longer than thus far assumed.

Okabe et al. (71) examined the factors that affect the occurrence of bacteremia associated with tooth extraction and the types of bacteria causing this bacteremia. 183 patients with one or more teeth extractions were included. Bacteremia was found in 132 patients (72.1%) who had one or more teeth extraction. Variables including sex, age, indication of tooth extraction, number of teeth extracted, duration of operation, and volume of blood lost during operation were evaluated. They found that bacteremia occurred more frequently when teeth were extracted because of inflammatory dental diseases. Furthermore, the occurrence of bacteremia increased with the number of teeth extracted and the age of the patients. When the volume of blood lost during surgery was more than 50 ml and the time required for the operation > 100 minutes, the occurrence of bacteremia was also higher. Anaerobes were isolated from 104 (78.8%) of the 132 cases of bacteremia. Of the 187 isolates obtained, three (1.6%) were aerobes, 51 (27.3%) were facultative anaerobes, and 133 (71.1%) were anaerobes. Among facultative anaerobes and micro-aerophils, the most frequently isolated bacterial genera were *Lactobacillus, Streptococcus, Staphylococcus,* and among anaerobes, *Eubacterium, Peptostreptococcus,* and *Propionibacterium.* They concluded that bacteremia was very frequently associated with tooth extraction.

Takai et al. (103) determined the incidence and bacteriology of bacteremia associated with various oral and maxillofacial surgical procedures. 237 patients who were underwent oral and maxillofacial surgeries were included in this study. Blood samples were obtained for bacteriological examination immediately after the essential steps of the surgical procedure had been performed. In this study, bacteremia was detected in patients who underwent surgery for tumor, infection and trauma, and surgical reconstruction of jaw. In particular, decortication for osteomyelitis and tooth extraction resulted in a higher incidence of bacteremia compared with other surgical procedures. The incidence of bacteremia was not affected by oral hygiene, gingival inflammation, blood loss, and duration of surgery. Furthermore, concerning tooth extraction, there was no statistical difference in the incidence of bacteremia with respect to the number of teeth extracted and the method of extraction. Extraction of teeth with odontogenic infection (periodontitis, peri-apical infection, and peri-coronitis) did, however, produce a significantly increased incidence of bacteremia compared with infection-free teeth. *S. viridans* were the predominant group of bacteria isolated from the bacteremias. They concluded that oral and maxillofacial surgeries involving trans-oral incision produce bacteremia regardless of the extent and degree of surgical invasion. In particular, surgical procedure at infected sites is more likely to result in bacteremia compared with infection free sites. Therefore, complete examination and enough evaluation should be done for each patient and periodontist should be aware of the recommendations in this field and undertake the required precautions to protect their patients.

Heimdahl et al. (37) studied bacteremia by using lysis-filtration method with subsequent aerobic and anaerobic inoculation after dental extraction, third-molar surgery, scaling, endodontic treatment, and bilateral tonsillectomy. Samples were obtained before, during, and 10 minutes after treatment. Bacteremia was observed in 100% of patients after dental extraction, 55% of patients after third-molar surgery, 70% of patients after dental Sc, 20% of patients after endodontic treatment, and 55% of patients after bilateral tonsillectomy. Anaerobic microorganisms were isolated more frequently than aerobic microorganisms, and *S. viridans* group were the most commonly isolated bacteria. Ten minutes after treatment, the frequency as well as the magnitude of bacteremia showed pronounced reduction. From the results of their study

they concluded that after different oral surgical procedures, aerobic and anaerobic bacteremias are more frequent and appear in higher magnitudes than previously reported.

In order to prevent or decrease the occurrence of bacteremia, researchers started to use different methods before or during dental procedures including antibiotic prophylaxis, mouthrinsing, and subgingival irrigation with antiseptic mouthwashes. Roberts et al. (86) studied the effects of amoxicillin on the incidence of bacteremia after dental extraction. The study included two groups of children (control group and test group). In the test group, each child had received oral amoxicillin 50 mg per kg body weight. Bacteremia following extraction was detected in 18 out of 47 (38 %) controls but in only one out of 47 (2%) antibiotic receiving patients. Bacterial isolates were usually sensitive to amoxicillin. They concluded that oral amoxicillin 50 mg/kg body weight would almost eliminate odontogenic bacteremia. This study demonstrated the advantages of pre-procedural use of amoxicillin as a prophylactic antibiotic for the prevention of bacteremia and subsequent IE.

Coulter et al. (15) determined the incidence and intensity of post extraction bacteremia in children with relation to the number and types of teeth extracted, oral hygiene, gingival health, and the presence of dentoalveolar abscesses. In addition, they assessed the efficacy of penicillin, amoxicillin, and erythromycin in the prevention of bacteremia. The incidence and intensity of bacteremia following tooth extraction in children were measured by blood culture. Fifty-eight healthy pediatric patients aged 2 to 13 years (mean age 7 years) attending an out-patient clinic for dental extraction under general anesthesia were enlisted in the study and were divided into two groups. The first group was selected randomly and consisted of 26 children with known cardiac abnormality who were at risk from IE and required antibiotic prophylaxis. Thirty-two non-cardiac patients comprised the second group and were selected to balance the cardiac group with respect to the number of teeth required extraction. Teeth were extracted with minimum trauma. The 26 children at risk from IE were given one of the following four antibiotics regimens: intra-muscular (im) penicillin (8 patients), oral amoxicillin (8 patients), intra-venous (iv) amoxicillin (6 patients), or iv erythromycin (4 patients).

They found that the antibiotic prophylaxis reduced the incidence of bacteremia from 63 % to 35 %. The intensity of bacteremia was 2 colony forming unit or less in 80% of the children. An agar pour-plate method of blood culture was significantly more effective than broth in culturing the small volumes of inoculum. In pour-plate method, 83 bacterial strains were isolated. 39 were strict anaerobes or micro-aerophilic and the remainder were *Streptococci*. There was no direct association between the plaque and gingival indices and incidence of bacteremia or between the number of teeth extracted and the incidence and intensity of bacteremia. They concluded that all children at risk of IE require antibiotic prophylaxis prior to tooth extraction since it is impossible for the likelihood or intensity of transient bacteremia to be clinically predicted. From this study, it can be concluded that the intensity of bacteremia is not correlated with the degree of gingival inflammation and the antibiotic prophylaxis is important to reduce such phenomenon.

Lofthus et al. (59) determined the incidence of bacteremia after a single professional subgingival irrigation with a 0.12% chlorhexidine (CHX) mouthwash alone and after a subsequent Sc/Rp during the same visit. Thirty patients each with at least one site that probed 4 mm or more and bled on probing were randomly assigned to three groups: irrigation with 0.12% CHX, irrigation with sterile water, and non-irrigated controls. To begin the study, blood was drawn just before and 2 min after irrigation. Thirty min later, blood was drawn again just before and 2 min after Sc/Rp at the same site. Blood samples were cultured for anaerobic and aerobic microorganisms using tryptic soy broth bottles culturing techniques. They reported that 18 blood cultures from 15 patients yielded positive cultures resulting in 23 isolates. In the CHX group, bacteremia was detected in 5 subjects after irrigation and in 2 other subjects after Sc/Rp. In the water group, bacteremia was detected in one subject after irrigation and in four subjects after Sc/Rp. The control group had three bacteremias after Sc/Rp. There was no significant difference between the incidence of bacteremia associated with irrigation with CHX or sterile water. In addition, there was no significant difference in the incidence of bacteremia after Sc/Rp between CHX and sterile water irrigation groups, and in patients who did not receive irrigation (control group). They concluded that sub-gingival irrigation, with or without CHX, had no effect on the incidence of bacteremia following

a subsequent Sc/Rp; furthermore, irrigation by itself could induce bacteremia as other dental manipulations. Therefore, irrigation might be considered as a safe procedure for healthy patients but not for risky patients.

Waki et al. (117) determined the effects of professional subgingival irrigation, together with subsequent patient administrated home marginal irrigation, on the incidence of bacteremia after Sc/Rp. Sixty periodontal maintenance patients were assigned to either Group 1: subgingival irrigation, with 0.12% CHX and daily marginal irrigation with 0.04% CHX; Group 2: subgingival irrigation with 0.12% CHX and daily marginal irrigation with water; Group 3: subgingival and daily marginal irrigation with water; Group 4: Non-irrigation (control). Patients entered the study after receiving a thorough periodontal maintenance appointment including a complete examination, Sc/Rp, and standard oral hygiene instruction. Blood samples were taken at the 3-month visit before and after Sc/Rp. Microbiological culturing was done using the Septi-Chek system, selective and non-selective media. Results showed that bacteremia was detected prior to Sc/Rp in two patients and after Sc/Rp in 10 patients. No significant effect by treatment regimens on post Sc/Rp bacteremia could be detected. The organisms detected included *Fusobacterium nucleatum, Propionibacterium acnes, Streptococcus* sp*, Neisseria* sp*, Candida albicans, Staphylococcus* sp, and un-identified Gram-negative rods. This study shows that the incidence of bacteremia after Sc/Rp in periodontal maintenance patients is low and sub-gingival irrigation with antiseptic mouthwashes have no effect on the incidence of bacteremia in such patients.

Fine et al. (27) examined the effect of subgingival irrigation and rinsing with an antiseptic mouthwash before US. Eighteen patients who showed previous bacteremia were included in their study. Patients were randomly assigned to an antiseptic mouthwash group or placebo control group. Ten ml of blood was withdrawn before the procedure, and then subgingival irrigation was performed followed by US. Immediately after the procedure, another 10 m1 blood sample was taken. For the test group, mean pre-treatment aerobic and anaerobic counts were 2.44 and 0.50 cfu/ml respectively. For the control group, mean pre-treatment aerobic and anaerobic counts were 3.22 and 1.78 cfu/ml. For the test group, mean post-treatment aerobic and anaerobic counts were 4.67

and 1.61 cfu/ml, respectively. For the control group, mean post-treatment aerobic and anaerobic counts were 38.62 and 14.89 cfu/ml, respectively. Overall, the antiseptic mouthwash resulted in aerobic counts that were 92.3% lower than those with the control mouthwash and anaerobic counts that were 87.8% lower. Theses differences were statistically significant ($p<.0001$). From this study, in contrast to waki's study (117) it can be concluded that pre-procedural rinsing and subgingival irrigation could significantly reduce the level of bacteremia associated with US.

Rahn et al. (79) compared the efficacy of povidone-iodine and CHX to prevent post extraction bacteremia. Before extraction, subgingival irrigation of the affected sites was done with either undiluted povidone-iodine (10%), 0.2% CHX, or water. The frequencies of bacteremia detected after irrigation were as follows: povidone-iodine 27.5 %; CHX 45 %; and water 52.5 %. They identified 206 isolates. 87 in the control group, 42 in the povidone-iodine group, and 77 in the CHX group. The most frequently isolated bacteria were *S. viridans*. They concluded that the irrigation of the gingival sulcus with povidone-iodine solution can produce a significant reduction in the incidence of bacteremia and therefore might reduce the number of cases of IE occurring after dental treatment in high-risk patients.

Root canal treatment is one of the dental procedures which may also induce odontogenic bacteremia. Debelian et al. (20) characterized oral microorganisms believed to have spread from the root canal into the blood stream during and after endodontic therapy of teeth with asymptomatic apical periodontitis. Microbiological samples were taken under aseptic conditions from the root canal of 26 single-rooted teeth in 26 patients. In the endodontic treatment of 13 of patients (Group 1), the first 3 reamers, size 15, 20, and 25, were used to a level of 2 millimeter beyond the apical foramen. In the other 13 patients (Group 2), the instrumentation ended inside the root canal 1 mm short of the apical foramen. Blood samples were taken from the patients during the instrumentation and 10 min after the treatment. Anaerobic microorganisms were isolated from all root canals. In 7 patients of group 1, *P. acnes, Peptostreptococcus prevotti, F. nucleatum, P. intermedia* and *Saccharomyces cerevisiae* were recovered from the blood. In 4 patients of Group 2, *P. intermedia, A. israelii, S. intermedius* and *S. sanguis* were isolated from the blood. Biochemical tests

and antibiograms revealed that the isolates from the root canal and blood had identical profiles within the patients, strongly suggesting that the microorganisms isolated from the blood had the root canal as their source. Therefore, it should be beared in mind that root canal treatment is one of the dental procedures that can induce bacteremia and enough precautions should be taken during performing this procedure in high-risk patients.

Bacteremia frequently occurs even after less invasive dental procedures such as orthodontic treatments. Erverdi et al. (25) assessed the incidence of bacteremia after orthodontic banding. Their study was conducted on 40 healthy orthodontic patients with good oral hygiene. Venous blood sample were obtained with a strict aseptic technique before and after fitting of a molar band in each patient. Microbiologic evaluation of the samples revealed a postoperative bacteremia incidence of 7.5 %. They concluded that orthodontic banding is one of the dental procedures which may induce odontogenic bacteremia.

In an other study, Erverdi et al. (23) investigated the prevalence of bacteremia after orthodontic banding and debanding following the application of 0.2% CHX. The banding and debanding groups were each composed of 40 young adult patients. In the banding group, patients were asked to rinse their mouths with CHX gluconate for 60 s just prior to fitting the bands. In the debanding group, patients were asked to rinse their mouths with CHX immediately before removal of the bands and brackets. In both groups, pre and post treatment blood samples were obtained with a strict aseptic technique. In the banding group, no bacteremia was detected in the pretreatment samples. Bacteremia was detected in 2.5% of post-treatment samples. In the debanding group, 2.5% bacteremia was found in both the pre- and post-treatment samples. They concluded that the application of CHX mouthwash resulted in a decrease in the prevalence of bacteremia after banding and debanding but the decrease was not statistically significant.

3.3.9. Prophylaxis of Odontogenic Bacteremia

Antibiotics are the mainstay of treatment of odontogenic bacteremia and often used before positive identification of the bacteria is made. Since 1955, antibiotic prophylaxis has been advocated to prevent such serious phenomenon (73). As they are given prior to dental treatment, they may prevent bacteremia in some clinical situations with the caveat that it is impossible to predict which patient will develop bacteremic infection and the risk associated with a particular treatment procedure (53, 111). In addition, a prolonged incubation period after initial colonization can make it difficult to determine whether an infection results from a specific dental procedure-induced bacteremia or from spontaneous bacteremia associated with daily living. Moreover, frequent use of antibiotic prophylaxis makes the treatment more expensive and may trigger adverse reactions such as hypersensitivity, blood disorders, gastrointestinal problems, bacterial resistance, and interactions with other drugs.

The antibiotics including ampicillin, amoxicillin, and penicillin V are equally effective *in vitro* against *a-hemolytic Streptococci*. However, amoxicillin is recommended because it is absorbed by the gastrointestinal tract and provides higher and more sustained serum levels. The recommended dose of amoxicillin previously was 3.0 g taken 1 hr before the procedure and then 1.5 g taken 6 hr after the initial dose (28). Recent comparisons of 2.0 g and 3.0 g dosing indicate that a 2.0 g dose results in adequate serum levels for several hr and causes less gastrointestinal adverse effects (15). The newly recommended adult dose is 2.0 g of amoxicillin (pediatric dose is 50 mg/kg not to exceed the adult dose) to be administered orally 1 hr prior to the procedure. A second dose is unnecessary both because of the prolonged serum levels above the minimal inhibitory concentration of most oral *Streptococci* (16) and the prolonged serum inhibitory activity induced by amoxicillin against such strains (6-14 hours) (28).

Although antibiotic prophylaxis is recommended to prevent odontogenic bacteremia during and after dental procedures by AHA, IE and other bacteremia related complications are not completely prevented. Therefore, usage of mouthwashes, especially CHX, in addition to the antibiotic prophylaxis prior to the dental procedures

is also recommended by AHA (23, 27, 59, 79). Useful agents may include chloramines-T, povidone-iodine, iodine and glycerin, and CHX (40). The clinical and microbiological advantages of using antimicrobial agents as coolants during US are may not be ignored (29, 88, 102). In an effort to reduce the incidence and severity of bacteremia during US, we used the antiseptic mouthwashes as a coolant in addition to usage of them as mouthwashes in our study.

3.3.10. Recommendation of the American Heart Association

Certain more or less aggressive oral and/or dental interventions and even routine activities in the mouth have been known to produce bacteremia. However, bacteremia induced by dental procedural interventions would be more important in creating complications which are considered of high morbidity and mortality for high-risk patients. Therefore, antibiotic prophylaxis is deemed necessary prior to dental treatment procedures of such patients (17). Recommendations of the AHA for antibiotic prophylaxis for cardiac morphologic alterations and related procedures are shown in Table 4 and 5.

Table 4. Recommendation of the American Heart Association for Antibiotic prophylaxis. Cardiac morphologic alteration (17).

High Risk (Prophylaxis Recommended)	Moderate Risk (Prophylaxis Recommended)	Low Risk (Prophylaxis Unnecessary)
• Heart valve prosthesis • Prior history of IE • Congenital disease with cyanosis (T. of Fallot, single ventricle, transposition of the great vessels) • Shunts	• Other congenital diseases (patent arterial duct, persistent ostium primun, aortic coarctation, bicuspid aortic valve) • Acquired valve dysfunction (rheumatic cardiac disease, type II collagenopathies) • Mitral valve prolapse with regurgitation • Hypertrophic myocardiopaty	• Internal communication like ostium secundum • Surgical intervention of interatrial communication or patent arterial duct • History of coronary artery by-pass surgery • Mitral valve prolapse with no regurgitation • Physiologic functional or innocent heart murmurs • Prior Kawasaki disease with no valve dysfuntion • History of rheumatic fever with no valve dysfunction • User of pacemaker or cardiac defibrillator

Table 5. Recommendation of the American Heart Association for Antibiotic prophylaxis. Dental procedures (17).

Prophylaxis Recommended	Prophylaxis Unnecessary
• Dental extraction and oral surgery • Periodontal treatment (surgery, Sc/Rp) • Prior to shaping down teeth to create abutments • Placement of Osseointegrated implants • Reimplantation • Surgery or endodontic instrumentation • Apicectomy • Subgingival placement of antibiotic • Placement of orthodontic bands • Intraligamentary local anesthesia • Pre-prosthetic surgery • Prophylactic cleaning of teeth. • Placement of immediate prosthesis • Placement of matrex bands • Puncture, drainage of infected tissues	• Operative dentistry • Placement of clamps and rubber dams • Placement of posts • Postoperative suture removal • Placement of prosthesis • Placement of orthodontic appliances • Local anesthetic injection (non-Intraligamentary) • Fluoride treatments • Fissure sailing • Oral radiograph • Orthodontic appliance adjustment

3.3.10.1. Prophylactic Regimens

Despite the relationship between dental treatment procedures and IE is not certainly defined, antibiotic prophylaxis for high-risk patients is still recommended (17, 30, 92). Antibiotic prophylaxis is most effective when given preoperatively in doses that are sufficient to assure adequate antibiotic concentration in the serum during and after the procedure. Antibiotics should be initiated shortly before the procedure and should not be continued for an extended period (not more than 6 to 8 hr) (30). In the case of delayed healing, or of a procedure that involves infected tissue, it may be necessary to provide additional doses of antibiotics for the treatment of established infection (30). Regimens for dental and oral procedures are shown in Table 6.

Table 6. Recommendation of the American Heart Association for antibiotic prophylaxis. Regimens for dental procedures (17)

Situation	Agent	Regimen
Standard prophylaxis	Amoxicillin	Adults: 2 g oral 1 hr before Children: 50 mg/kg 1 hr before
No oral administration	Amoxicillin	Adults: 2 g im or iv 30 min. Before Children: 50 mg/kg im or iv 30 min. before
Allergy to penicillin	Clindamycin/	Adults: 600 mg oral 1 hr before Children: 20 mg/kg oral 1 hr before
	Cephalexin/ Cefadroxil	Adults: 2 g oral 1 hr before Children: 50 mg/kg oral 1 hr before
	Azithromycin/ Clarithromycin	Adults: 500 mg oral 1 hr before Children: 15 mg/kg oral 1 hr before
Allergy to penicillin no oral admin.	Clindamycin	Adults: 600 mg iv 1 hour before Children: 20 mg/kg iv 1 hr before
	Cefazolin	Adults: 1 g im or iv 30 min. before Children: 25 mg/kg im or iv 30 min before

3.4. Antiseptic Mouthwashes

The mouthwashes are antimicrobial products that can help in the control of microorganisms that cause disease activity. They are an important aspect of periodontal treatment because they can reach the site of bacterial infection, so, can be used as adjuncts with mechanical methods for elimination of pathogenic microorganisms (40). American Dental Association has accepted some mouthwashes for the use in the treatment of periodontal diseases. Useful agents may include chloramines-T, povidone-iodine, iodine and glycerin, and CHX (40). In our research, we selected relatively new mouthwash, Biotene (BIO) since BIO does not have any side effects as in CHX.

3.4.1. Biotene Mouthwash

It is an alcohol-free mouthwash and strong antimicrobial system designed to enhance the antibacterial flora of the oral cavity. It effectively reduces the complications of xerostomia by cleaning and refreshing without burning and by neutralizing mouth

odors. BIO is a strong antibacterial system which works by splitting the cell wall of pathogenic bacteria and depriving them of iron (112, 116). It contains the same exact enzymes naturally produced by the mouth to work against harmful bacteria and to help in protecting teeth and gingiva (55). These enzymes are lysozyme, lactoferrin, glucose oxidase and lactoperoxidase system (lactoperoxidase, thiocynate ions, and hydrogen peroxide). Among these, lysozyme splits the cell wall of pathogenic bacteria. Lactoferrin is an iron-binding protein which inhibits pathogenic bacteria by depriving them of iron. Others function by obtaining highly oxidizing environment by oxidizing the glucose and lactase. BIO contains also some inactive ingredients including water, xylitol, hydrogenated starch, propylene glycol, hydroxyethylcellulose, aloe vera, natural peppermint, poloxamer 407, calcium lactate, sodium benzoate, and benzoic acid. The combination of these natural ingredients creates a salivary enzyme system that helps to maintain a healthy balance of oral flora reducing harmful bacteria while sustaining beneficial bacteria.

3.4.1.2. Effect of Biotene on Oral Flora

Lysozyme works on both gram-positive and gram negative organisms but it is more effective against *Veillonella* and *A. actinomycetemcomitans*. Lactoferrin is effective against *Actinobacillus* sp. The combination of lactoperoxidase, thiocynate ions, and hydrogen peroxide forms a bacteriostatic system. Lactoperoxidase catalyzes the oxidation of thiocynate ions by hydrogen peroxide to yield the antimicrobial oxidizing agents hypothiocyanous acid and hypothiocyanite ions (108, 112). Clinical and laboratory evidences suggest that a lactoperoxidase containing enzyme system acts as an antimicrobial factor in the oral cavity having a role in the prevention of dental plaque accumulation, dental caries, and gingivitis (41, 43, 49, 55, 65, 68, 78). Tenovuo et al. (105) proved that supplementation of saliva with an appropriate combination of thiocyanate and hydrogen peroxide resulted in a significant increase in the concentration of hypothyiocyanite ions and more effective for inhibition of plaque acid production. Among the oral defense factors, the salivary lactoperoxidase system seems to play an important role by producing highly reactive antibacterial products that can regulate bacterial metabolism in the human mouth. Toljanic et al. (112) in a double blind

crossover trial assessed the efficacy of dentifrice containing salivary peroxidase elements in the reduction of gingivitis in a population of patients with irradiated cancer. Subjects were instructed to use the dentifrice provided. Plaque and gingival index values were obtained, and statistically compared with baseline values. A positive effect was found between the use of dentifrice and the reduction of gingival inflammation. The results suggested the positive efficacy for the dentifrice in augmenting traditional measures of post-radiation oral health maintenance. In another study performed by University Of Southern California School Of Dentistry and Laclede research Laboratories (68), they tested the antimicrobial property of BIO versus placebo and found out that there was an average of 63.8% inhibition after 4 hr of the total viable counts in the BIO group. They also tested the minimal inhibitory concentration of selected microorganisms. The results showed that only *P. intermedia* were totally inhibited. *Lactobacillus acidophilus*, *P. gingivalis, A. actinomycetemcomitans*, and one isolate of *F. nucleatum* exhibited slight growth.

3.4.2. Chlorhexidine

CHX has been widely investigated as a topically applied antibacterial agent and has worldwide acceptance as an effective antiplaque and antigingivitis agent (3).

3.4.2.1. Clinical Efficacy of Chlorhexidine

CHX gluconate is used as an antiseptic for skin wounds, preoperative skin and mouth preparations, postoperative surgical oral procedures, and as an antimicrobial agent for inhibition of microbial dental plaque and development of gingivitis (3). It has a broad antimicrobial action including a wide range of gram-positive and gram-negative bacteria. CHX is available as 0.12% and 0.2% solution without any significant differences in the antimicrobial effects or in the clinical efficacy between the two concentrations (40). CHX activity in the oral cavity is promoted its ability to adhere to hard and soft tissues and then released after a time (*substantivity)* allowing antimicrobial activity to continue over 6 hr or more (13). The plaque inhibiting activity shown by CHX is a property demonstrated by rupturing bacterial cell membranes by cationic bis-biguanide.

Considerable evidence has been accumulated indicating that retention of CHX in the mouth is the basis for the plaque inhibition property (12). About 30% of the CHX introduced in the mouth during a mouthrinse is retained. The teeth are not the major retention site, at least not quantitavely, but plaque covered teeth have been shown to bind limited quantities of the agent. Results of studies that used mouthwashes at different pH levels strongly indicate that acidic groups presumably on the macromolecules of the mucus secretions covering the oral surfaces are the receptors responsible for the major share of the retained CHX. Electrostatic binding between the acidic protein group and the basic bis-biguanide molecules seem to be involved (13). AHA recommends CHX irrigation of the gingival sulcus or painting CHX on isolated dried gingiva for 3-5 minutes before treatment (123). However, Lofthus et al. (59) found no difference in the magnitude of bacteremia after Sc/Rp for patients given subgingival irrigation with CHX, saline or controls. Ordinarily, CHX might be used prior to dental treatment after the systemic antibiotic prophylaxis has reached adequate blood levels, but CHX alone without systemic prophylaxis may be appropriate in low risk patients.

3.4.2.2. Side Effects of Chlorhexidine

Despite the excellent plaque inhibitory properties of CHX, widespread and prolonged use of this agent are limited by its local side effects. These side effects include calculus formation, desquamation of gingiva, inflammation of salivary glands ducts, mucositis, mucosal erosion, taste alteration and staining of teeth porcelain. In addition, it is of limited value in the therapy of established oral conditions including gingivitis because it is cationic in nature (poor penetrability) and is much more valuable in the penetrative mode. Moreover, sustained or frequent usage of CHX may not be recommended as this may result in selection of resistant S*treptococci*, enteric gram-negative rods, *Pseudomonas* and *Enterococci*. These organisms can colonize the oral cavity and induce a type of endocarditis associated with even higher mortality rate than the *S. viridans* (40, 81, 98).

4. AIMS

Although antibiotic prophylaxis is recommended to prevent odontogenic bacteremia during and after dental procedures by AHA in 1980 for high risk patients, IE or other bacteremia related complications are not completely prevented. Therefore, the usage of mouthwashes, especially CHX, in addition to the antibiotic prophylaxis prior to the dental procedures is also recommended by AHA in 1986. To date, the most popular mouthwash used for this purpose is CHX and no other mouthwashes has been demonstrated to be as effective and easy to use as CHX. Since the use of CHX is not always preferred due to its side effects, the primary goal of the presented study was to evaluate the effectiveness of a relatively new mouthwash, BIO in preventing US related bacteremia, and to compare its efficacy with CHX. The usage of mouthwash as a coolant in addition to its use as a mouthrinse was further added to the methodology to increase the effectiveness of related mouthwash which was the first time in the literature of the bacteremia related studies.

5. MATERIALS & METHODS

This project was approved by the ethical committee of Institute of Health Sciences, Faculty of Medicine, Marmara University. All the procedures were explained to the patients and each individual signed an informed consent form as soon as they decided to participate in the study.

5.1. Patient selection

This study comprised 30 patients (19 males and 11 females) who were referred to the Department of Periodontology at Faculty of Dentistry, Marmara University for periodontal treatment. All patients met the diagnostic criteria of plaque-induced gingivitis with plaque and gingival index not less than 1.5 and exhibited no interproximal bone loss on radiographic assessments. They were divided into 3 groups and each group comprised 10 patients. BIO[1] group included 3 males and 7 females; 0.2% CHX gluconate[2] group included 8 males and 3 females; and normal saline group as a control group (C) included 8 males and 2 females. Average ages of the patients in the three groups were 25.5, 26.9, and 25.7 years, respectively.

All subjects were systemically healthy, required to have at least 20 natural teeth, and no history of periodontal therapy. Patient exclusion criteria were the following: antibiotic therapy within the previous 3 months, usage of antiseptic mouthwash, acute pulpal or peri-apical infection, pregnant or lactating women, history of IE, congenital or acquired cardiac defect, cardiac prosthesis, hematological disorders, immune defects, corticosteroid or immunosuppressive medication, or any systemic conditions that might effect the periodontium and the experimental protocol.

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[1] **Biotene,** Laclede, Inc. Rancho Dominguez, USA.
[2] **Klorhex**, Drogsan, Ankara, Turkey.

5.2. Study Design

Ten subjects were assigned to each of 3 treatment groups: BIO group, 0.2% CHX group, and control group. Oral hygiene instructions were given and clinical measurements were taken 7 days before the experimental day. At the experiment day, a baseline 11 ml of blood was drawn (24, 25) from the antecubital vein (76) followed by mouth rinsing for 60 s (23) with the appropriate mouthwashes for each group. After 4 min (27, 67), US was performed for 1 min. Immediately after the US, the second blood sample was drawn (17). Then, after the exact waiting period of 5 min and 10 min from starting of the US, 11 ml of blood was drawn at each step. All blood samples were immediately inoculated into blood culture bottles and were taken to the microbiology laboratory. Clinical measurements were repeated at 3 months post treatment. The steps of the study are summarized in Figure 1.

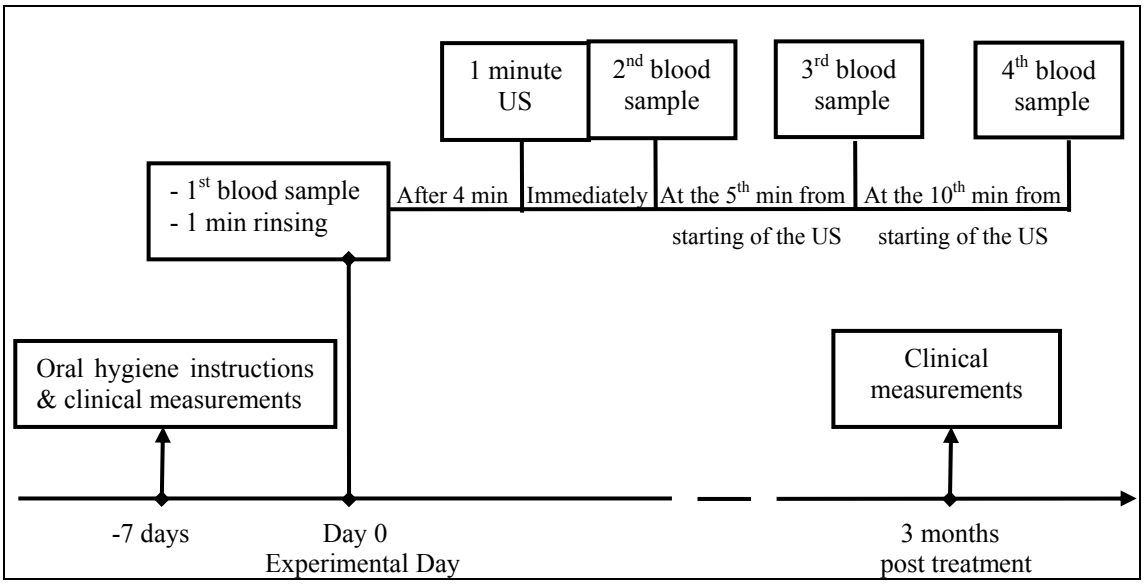


Figure 1. Study design

5.3. Clinical Indices and Measurements

For all patients, the following clinical parameters were measured pre- and post-operatively by using an explorer and the UNC-15 periodontal probe[3] and recorded in the data sheet prepared for the thesis (Figure 2).

[3] **PCP 15 UNC**, Hu-Friedy, Chicago, IL, USA.

Marmara University Faculty of Dentistry
Department of Periodontology
Master Thesis Propgram
Data Sheet

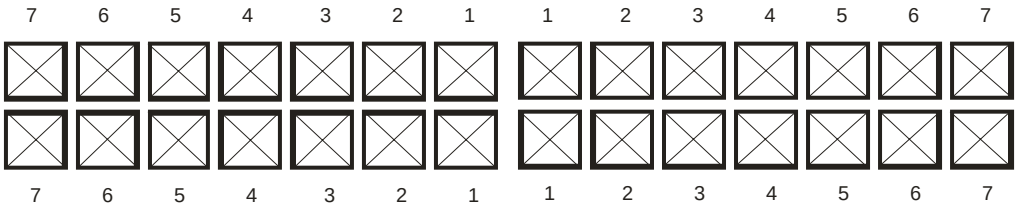
Master Student Name: Mohamed Ihwigat **Supervisor: Assist. Prof. Dr. Kemal Kose**

Patient's Name and Surname:

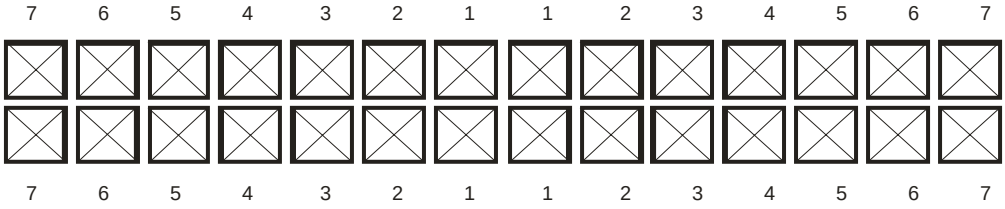
Age: **Date:**

Study Group: **Measurement Period:**

Plaque Index



Gingival Index



Probing Pocket Depth

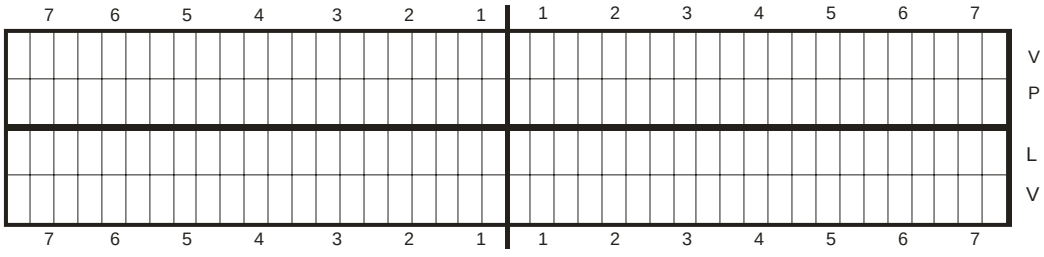


Figure 2: Thesis data sheet

5.3.1. Plaque Index

The microbial dental plaque on the teeth surfaces was evaluated by the explorer in four areas of mesio-buccal, mid-buccal, disto-buccal, and mid-lingual and scores between 0-3 were given for each point according to the criteria of the plaque index shown in Table 7. To determine the plaque index (PI) of each tooth, the scores of four areas were summed and divided by 4. To determine the PI of each patient, the plaque scores of the teeth were summed and divided by number of teeth (94).

Table 7. Criteria for the plaque index (94)

Score	Criteria
0	No plaque in the gingival area
1	No plaque visible by the unaided eye, but plaque is made visible on the point of the probe after it has been moved across surface at entrance of gingival crevice
2	Gingival area is covered with a thin to moderately thick layer of plaque; deposit is visible to the necked eye
3	Heavy accumulation of soft matter, which fills the gingival margin and tooth surface; interdental area is stuffed with soft debris

5.3.2. Gingival Index

The gingival tissues were assessed using gingival index (GI), as a method for assessing the severity of gingival inflammation (61). On both buccal and lingual surfaces of each tooth, mesial and distal papilla areas and the mid points were examined. Bleeding was assessed by running a periodontal probe parallel to the long axis of each tooth along the soft tissue wall of the gingival crevice. Scores between 0-3 were established according to the criteria of the GI shown in Table 8. The scores of four areas were summed and divided by 4 to determine the GI of each tooth. To determine the GI of each patient, the plaque scores of the teeth were summed and divided by number of teeth.

Table 8. Criteria for the gingival index (61)

Score	Criteria
0	Normal gingiva
1	Mild inflammation: slight change in color, slight edeme, no bleeding on probing
2	Moderate inflammation: redness, edema and glazing, bleeding on probing
3	Sever inflammation: marked redness and edema, ulceration; tendency toward spontaneous bleeding

5.3.3. Probing Pocket Depth

PPD were measured as the distance between the free gingival margin and the probable bottom of the pocket, and determined by means of the periodontal probe in a total of 6 points in each tooth (Mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual).

5.4. Experimental Procedure

At the experiment day, all patients were asked not to brush their teeth, eat, or chew gum for at least 2 hr prior to their appointments for the blood drawing (23).

5.4.1. Blood Sampling

For each patient, prior to blood sampling, the skin of the cubital fossa was carefully cleaned and wiped with alcohol. A 22 gauge sterile plastic cannula[4] was placed in the antecubital vein (Picture 2a). An initial 11 ml blood specimen was drawn into a sterile syringe prior to any oral manipulation as a baseline in each subject (Picture 2b). After finishing blood withdrawal, the valve of the cannula was carefully closed to avoid contamination. Immediately after 1 min Sc, the valve of the cannula was

[4] **BD Veflon,** Bacton Dickinson Co., Helsingborg, Sweden.

reopened and the second blood sample of 11 ml was drawn into a new sterile syringe. The third blood sample was drawn at the fifth min from starting the US. The fourth blood sample was drawn at the tenth min from starting of US. For each sample, blood withdrawal was completed within 30 s.

	
Picture 2a	**Picture 2b**

Picture 2a: Plastic cannula placed into antecubital vein
Picture 2b: Blood withdrawal through antecubital vein

In the case of inability to find the antecubital vein, prolonged blood sampling time, inability of some patients to continue because of the cannula, and fainting the patients were discharged from the study.

5.4.2. Mouth Rinsing

After the first blood sample was drawn, each patient has done mouth rinsing for 60 s, using 15 ml of the appropriate mouthwash for each group.

5.4.3. Ultrasonic Scaling

Four min following mouth rinsing, waiting time for adequate effect of used mouthwash, US was performed by ultrasonic scaler[5] with curved metal tips. US lasted for one min; the _____

[5] Piezon Master, EMS, Nyon, Switzerland

tip of the scaler was applied parallel to the tooth surface to remove the supra- and sub-gingival debri, and with the intention of no traumatization to the soft tissues. During US, the used coolant was the respective agent used for mouth rinsing (BIO, 0.2% CHX, or normal saline) according to the group. Full mouth Sc for each patient was completed right after the completion of the experiment.

5.5. Laboratory Procedures

Ten ml of pre- and post-operative blood samples were aseptically inoculated into Signal Blood Culture (SBC) bottles[6] (Picture 3a-b). The name, date, and code numbers of the patients were recorded on each bottle to keep track of the results. Each bottle was then connected with a growth indicator device (Picture 3c-e) and incubated at 37 °C for 14 days. Positive results were indicated from the bottles in which the blood/broth mixture had risen above the green locking sleeve of the growth indicator device (Picture 3f).

Whenever a bottle gave a positive signal, samples were taken from positive bottles using sterile loops and plated on trypticase soy agar supplemented with 5% sheep blood, and trypticase soy agar supplemented with 5% sheep blood, 0.0005% hemin[7], and 0.00005% menadione[8] within less than 24 hr to identify the present sp (Picture 3g-j). These were incubated under aerobic and anaerobic conditions. Aerobic incubation lasted 4 days at 37 °C. The anaerobic samples were placed into jars containing anaerobic atmosphere and were incubated at 37 °C for 7 days. The anaerobic medium inside the jars was obtained by using kits[9] incubation. Bacterial sp (Picture 3k) were identified by colony morphology, gram-staining procedures, aerotolerans, using standard microbiologic biochemical testing technique, and API 20 strips[10] (Picture 3l).

Bottles that continued to show a negative level were discarded at the 14th day of incubation.

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[6] **Signal Blood Culture system,** Oxoid Unipath Limited, Hampshire, England.
[7] **Sigma Chemical Co**., St Louis, MO, USA)
[8] **Sigma Chemical Co.**
[9] **AnaeroGen**, Oxoid Unipath Limited, Hampshire, England.
[10] **BioMerieux SA,** Marcy, l'Etoile, France.

			
Picture 3a	**Picture 3b**	**Picture 3c**	**Picture 3d**
			
Picture 3e	**Picture 3f**	**Picture 3g**	**Picture 3h**
			
Picture 3i	**Picture 3j**	**Picture 3k**	**Picture 3l**

Picture 3a: Disinfection of the cover of bottle with alcohol to ensure aseptic technique

Picture 3b: Inoculation of 10 ml blood into the broth

Picture 3c: Insertion of the growth indicator device

Picture 3d: Blood/broth with growth indicator device

Picture 3e: Incubation of the blood/broth at 37°C

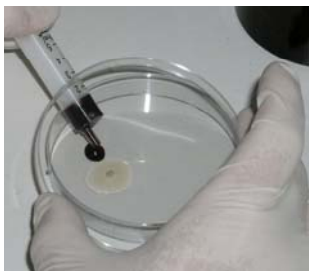
Picture 3f: Bottles with positive (right) and negative (left) results

Picture 3g-j: Cultures taken from positive samples being plated on both aerobic and anaerobic blood agar

Picture 3k: Bacterial colonies

Picture 3l: API 20 strips for identification of bacterial species

In addition to SBC test, the number of bacteria per ml of blood was determined by the pour-plate (PP) technique that used 20 ml of fastidious anaerobic agar (Oxoid) supplemented with 5% calf serum (Picture 4a-c). 1 ml of drawn blood was poured in the bacterial culture plank. After incubation for 4 days, bacterial colonies from the PP were counted and identified using aforementioned procedure.

		
Picture 4a	**Picture 4b**	**Picture 4c**

Picture 4a-c: Pour-plate method to determine number of bacteria.

5.6. Evaluation of Clinical Data

For all the clinical measurements, the mean and standard deviations were determined for each patient before and 3 months after the treatment Statistical values were compared among the three groups.

5.7. Statistical Analysis

Statistical analysis was performed using GraphPad Prisma software program[11]. For the statistical evaluation of the clinical parameters before and 3 months after the treatment, paired *t*-test was used. Differences in the incidence of bacteremia between groups were analyzed by Kruskal Wallis test. Inter-group comparison was done by utilizing Dunn's multiple comparison test. Statistical significance level was established at $p<0.05$.

[11] **GraphPad Prisma** V.3 program for Windows.

6. RESULTS

6.1. Clinical Results

Plaque Index

Mean values and standard deviations of PI scores before and 3 months after treatment are presented in Table 9. The PI scores in BIO, CHX, and C groups showed no statistical significant difference at the base line. After 3 months, the PI scores in BIO, CHX and C group had a statistical significant decrease ($p<0.001$). Inter-group comparison of the changes showed no statistical difference among the 3 groups ($p>0.05$, Table 10). Figure 3 represents the PI scores before and 3 months after the treatment in each group.

Gingival Index

Mean values and standard deviations of GI scores before and 3 months after treatment are presented in Table 9. The GI scores in BIO, CHX, and C groups showed no statistical significant differences at the base line. After 3 months, the GI scores in BIO, CHX and C group had a statistical significant decrease ($p<0.001$). Inter-group comparison of the changes showed no statistical differences among the three groups ($p>0.05$, Table 10). Figure 4 represents the GI scores before and 3 months after the treatment in each group.

Probing Pocket Depth

Mean values and standard deviations of PPD scores before and 3 months after treatment are presented in Table 9. The PPD scores in BIO, CHX, and C groups showed no statistical significant differences at the base line. After 3 months, the PPD scores in BIO, CHX and C group had a statistical significant decrease ($p<0.001$). Inter-group comparison showed no statistical differences between the three groups ($p>0.05$, Table

10). Figure 5 represents the PPD scores before and at three months after the treatment in each group.

Table 9. Mean values (X) and standard deviations (SD) of clinical indices and measurements at base line and 3 months after therapy.

		BIO Group (X±SD)	CHX Group (X±SD)	C Group (X±SD)
PI	**Before Treatment**	1.93±0.134	1.89±0.110	1.95±0.118
	After Treatment	* 0.69±0.074	* 0.77±0.116	* 0.81±0.137
GI	**Before Treatment**	2.05±0.184	2.10.±0.141	2.41±0.151
	After Treatment	* 1.02.±0.103	* 1.09±0.074	* 1.14±0.107
PD	**Before Treatment**	1.88±0.157	1.94±0.084	1.97±0.140
	After Treatment	* 1.60±0.157	* 1.76±0.085	* 1.78±0.142

* $p<0.001$

Table 10. Mean values (X) and standard deviation (SD) of the inter-group comparison of PI, GI, and PPD.

	BIO (X±SD)	CHX (X±SD)	C (X±SD)	p
PI	1.93±0.13	1.89±0.11	1.95±0.12	0.12
GI	2.05±0.18	2.10±0.14	2.14±0.15	0.93
PD	1.87±0.16	2.04±0.08	2.02±0.14	0.61

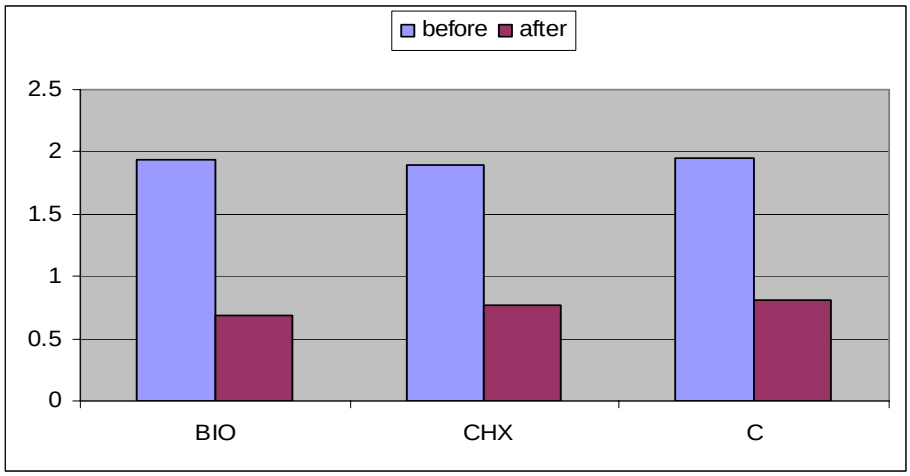


Figure 3. PI scores before and after treatment

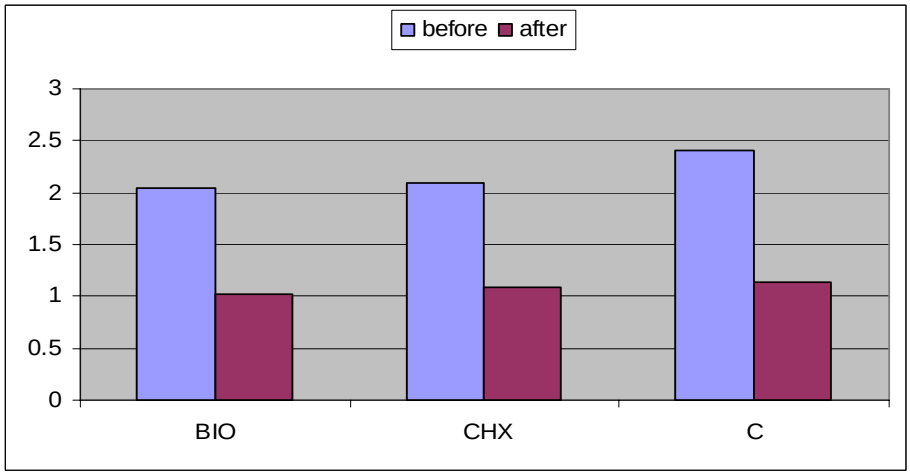


Figure 4. GI scores before and after treatment

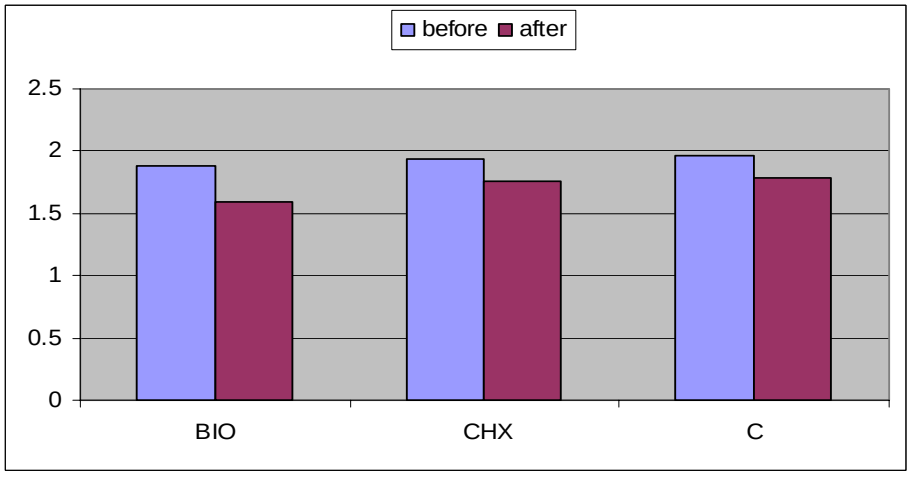


Figure 5. PD scores before and after treatment

6.2. Laboratory Results

6.2.1. Incidence of Bacteremia

For all of the patients of the three groups, pre-operative blood samples taken before US had negative blood cultures. The incidences of bacteremia for each group are presented in Table 11 and Figure 6.

In BIO Group

Bacteremia was found in the blood samples of four patients (40%), taken immediately after US (2nd samples). No any positive samples were found either at the 5th min samples (3rd samples) or at the 10th min samples (4th samples).

In CHX Group

Bacteremia was found in blood samples of three patients (30%), taken immediately after US (2nd samples). Only in 1 out of these 3 patients (10%), bacteremia was found at the 5th min samples (3rd samples) and the 10th min samples (4th samples).

In C Group

Bacteremia was found in blood samples of five patients (50%), taken immediately after US (2nd samples). For the same patients (50%), positive results were also found at the 5th min samples (3rd samples). Only in one out of these five patients (10%), bacteremia was found at the 10th min samples (4th samples).

The comparison of the three groups showed that both BIO and CHX had significantly reduced the incidence of odontogenic bacteremia ($p=0.011$, Table 11). On the other hand, there was no significant difference between the efficacies of BIO and CHX in reducing bacteremia (Table 12) even though the duration of bacteremia was longer in CHX group than in BIO group.

Table 11. Incidence of bacteremia (10 patients for each group)

Group	1st Sample	2nd Sample	3rd Sample	4th Sample
BIO Group	0%	40%	0%	0%
CHX Group	0%	30%	10%	10%
C Group	0%	50%	50%	10%
		p=0.011		

Kruskal Wallis test

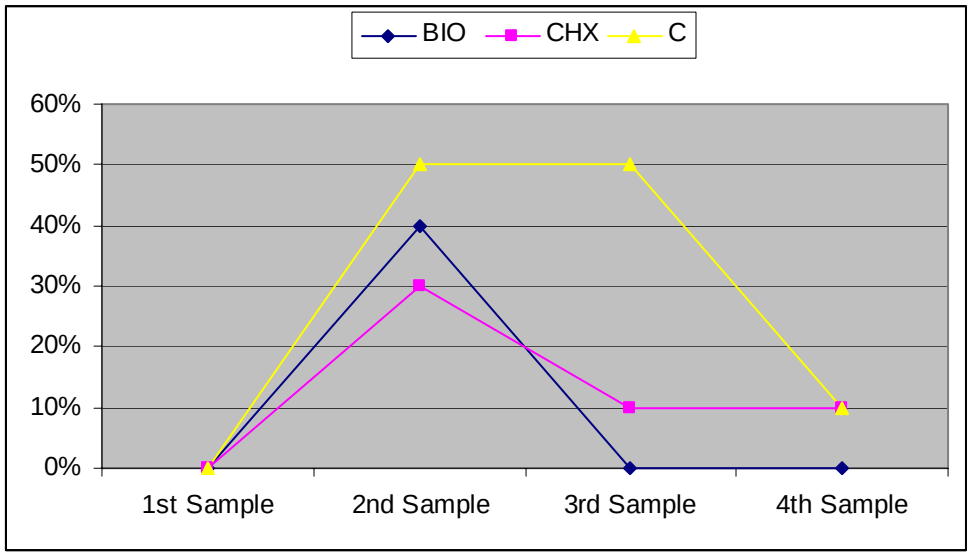


Figure 6. Incidence of Bacteremia

Table 12. Inter-group comparison (Dunn's multiple comparison test)

BIO / C	**P<0.05 ***
CHX / C	**p<0.05 ***
BIO / CHX	p>0.05

6.2.2. Bacterial Species

Detected bacterial sp in the blood circulation at different time points after US are shown in Table 13. In some positive samples, although the presence of bacteria was evident and we managed to distinguish the type of microorganisms, the number of microorganisms was so small that we could not detect any colony or growth to be counted in terms of cfu/ml. Total of 21 isolates were cultured in the positive samples of the study.

Streptococcus were the most common detected sp (61.90%); *S. salivarius* (33.33%), *S. mitis* (23.80%), and *S. sanguis* (4.76%). They were frequently recovered from the blood samples throughout the study. Other bacteria detected in this study were *Actinomyces* sp (23.80%) and *P. intermedia* (14.29%). Table 14 shows distribution of bacterial sp cultured from blood samples.

In BIO Group

Four out of 10 patients had bacteremia immediately after Sc (2nd samples) and among them, the identified microorganisms were *S. salivarius* with 26 cfu/ml in one patient. In one other patient, the identified microorganisms were *S. salivaris* and *Actinomyces* sp with 70 and 21 cfu/ml respectively. In the remaining two patients, the identified microorganisms for each of the patients were *S. sanguis* and *S. mitis,* respectively and no colonies were found to be counted regarding them.

In CHX Group

Three out of 10 patients had bacteremia immediately after Sc and the identified microorganisms for each patient were *S. salivarius* with 1 cfu/ml, *S. mitis* with 8 cfu/ml, and *S. salivarius* with no colonies, respectively. Out of these 3 patients, there was only 1 patient who had bacteremia at the 5th min (3rd samples) and 10th min sampling (4th samples). In this patient, the identified microorganisms were *S. salivarius* and neither of the samples (3rd and 4th) produced any colonies to be counted.

In C Group

Five out of 10 patients had bacteremia immediately after the US (2nd samples) and at the 5th min sampling (3rd samples); and in two of them, the identified microorganisms were *S. salivarius*. One of these two patients produced enough colonies to be counted which were 40 and 20 cfu/ml, respectively. In the other patient, the identified microorganisms were the *P. intermedia* with no colonies. And in the last two patients, which were positive, the identified microorganisms were *Actinomyces* sp with no colonies. Out of these 5 patients, there was only one patient who had bacteremia at the tenth min sample (4th samples). In this patient, the identified microorganisms were *P. intermedia* with no colonies to be counted.

Table 13. Distribution of cultivable organisms of patients

Patient's Code Number	Age	1st Sample (Before US)	2nd Sample (Immediately after US)	3rd Sample (5th min)	4th Sample (10th min)	CFU/ml
BIO1	22	-	*S. salivarius*	-	-	26
BIO2	24	-	-	-	-	-
BIO3	21	-	*S. salivarius*	-	-	70
			Actinomyces sp	-	-	21
BIO4	33	-	-	-	-	-
BIO5	25	-	*S. sanguis*	-	-	-
BIO6	25	-	*S. mitis*	-	-	-
BIO7	36	-	-	-	-	-
BIO8	26	-	-	-	-	-
BIO9	19	-	-	-	-	-
BIO10	24	-	-	-	-	-
CHX1	22	-	-	-	-	-
CHX2	34	-	*S. salivarius*	*S. salivarius*	*S. salivarius*	1
CHX3	23	-	-	-	-	-
CHX4	32	-	-	-	-	-
CHX5	25	-	-	-	-	-
CHX6	22	-	*S. mitis*	-	-	8
CHX7	28	-	-	-	-	-
CHX8	31	-	-	-	-	-
CHX9	37	-	-	-	-	-
CHX10	25	-	*S. salivarius*	-	-	-
C1	38	-	-	-	-	-
C2	19	-	-	-	-	-
C3	34	-	*S. salivarius*	*S. salivarius*	-	40, 20
C4	32	-	*S. salivarius*	*S. salivarius*	-	-
C5	23	-	*P. intermedia*	*P. intermedia*	*P. intermedia*	-
C6	18	-	-	-	-	-
C7	25	-	*Actinomyces sp*	*Actinomyces sp*	-	-
C8	28	-	*Actinomyces sp*	*Actinomyces sp*	-	-
C9	18	-	-	-	-	-
C10	22	-	-	-	-	-

Table 14. Distribution of bacterial species cultured from blood samples

Bacteria	Frequency	Percentage
Streptococcus sp	13	61.90
Streptococcus salivaris	10	47.61
Streptococcus mitis	2	9.52
Streptococcus sanguis	1	4.76
Actinomyces sp	5	23.80
Prevotella intermedia	3	14.30

7. DISCUSSION

Sc/Rp are known to cause damage to the gingival tissues leading to bacteremia (17, 27, 37, 48, 59, 79, 103, 117) which is a high risk factor for the development of IE in high-risk patients (42, 87, 100, 101). Management of these patients is a crucial matter in periodontics as well as in all fields of dentistry. In addition to the risk of IE, patients with synthetic vascular graft and prosthetic joints following dental procedures might be at risk (8, 26, 30, 73, 113). Therefore, prophylactic antibiotic regimens prior to dental treatment procedures are recommended for medically compromised high-risk patients (10, 83-85). While these regimens are largely successful, IE following dental manipulation could not be completely prevented (114). On the other hand, antibiotic prophylaxis cannot be prescribed on daily basis of all dental treatment procedures. Therefore, other methods must be introduced to decrease the total number of oral microorganisms in the mouth. AHA recommends antiseptic mouthwashes prior to dental procedures in order to reduce the incidence and severity of bacteremia (10). The results of published studies regarding the effect of using antiseptic mouthwashes on the incidence of odontogenic bacteremia have not shown any agent that can be used as an alternative to antibiotic prophylaxis. The usage of antimicrobial mouthwashes as a coolant in addition to usage of them as mouthwashes to prevent bacteremia during US has not been performed in previous bacteremia studies. The aims of our study were to investigate the effect of BIO mouthwash on the incidence of bacteremia associated with subsequent US; in addition, we compared the efficacies of BIO and 0.2% CHX gluconate in order to find out if BIO is as effective as CHX; moreover, we used antimicrobial agents not only as a mouthwash but also as a coolant during US in order to increase the antibacterial efficacies of mouthwashes which are the first time in the bacteremia studies in the literature.

The ability of detection of transient bacteremia depends on a number of factors. These factors include the site of blood withdrawal, timing of the blood sampling, blood volume, technique used for detection of the bacteremia, the degree of periodontal inflammation, and the quantity and the composition of the gingival flora (59, 91).

In the presented study, we investigated the incidence of bacteremia after US. Bacteremia occurs when bacteria enter the blood stream transiently by any reason and can be detected by laboratory blood culture techniques (87). The site of blood withdrawal is an important factor for detection of the bacterial sp that entered the blood. The number of microorganisms in the peripheral blood of a patient who is at risk of bacteremia is relatively small despite the fact that microorganisms appear to have free access to the circulating blood. This indicates that some mechanism is constantly at work to remove them from the blood. Opinions on the means of this removal have varied; some have considered a bactericidal action of the blood itself to be responsible while others have suggested that the circulating bacteria are arrested in particular parts of the body (118). If bacteria are removed from the blood in certain organs, one would expect to find fewer organisms in venous blood which has just passed through these organs than in the blood entering them. If a bactericidal action of the blood is responsible, there should be no marked difference in the bacterial content of the blood in different parts of the body. For clarifying the aforementioned hypothesis, Beeson et al. (5) compared sites of removal of bacteria from the blood of patients with bacterial endocarditis. In their study, blood was obtained from not only peripheral arteries and veins but also from such locations as the right auricle, the vena cava, hepatic, and renal veins. Blood collected from the antecubital fossa had colony counts only slightly lower than arterial blood. The femoral vein had appreciably less bacterial invasion and the hepatic vein had the smallest bacterial count. In our study, we choosed antecubital vein because this vein has colony counts only slightly lower than the arterial blood, easy for the patient, and it has been the preferred site in most researches for detection of odontogenic bacteremia in humans (4, 15, 16, 22, 24, 25, 48, 79, 80, 83, 95, 103).

Blood sampling time is another factor affecting the result of bacteremia studies. In some articles, blood sampling was performed 3 min before and after the completion of dental manipulation (4, 15, 18, 20, 24, 25, 27, 48, 64, 79, 80, 95, 103). Berger et al. (7) showed that blood samples taken immediately after extraction were 81.4% positive for bacteria but decreased to only 48.8% in cultures taken 10 min after extraction. Cobe (14) found that intravenous inoculations of *Streptococci* in rabbits were recovered in blood cultures taken by means of cardiac puncture at 1 min and 3 min. Minimal amounts were detected

after 5 min, and none after 10 min. Bender et al. (6) investigated the incidence of bacteremia after two dental procedures, light Sc endodontic treatment. In the light Sc group, positive results were observed immediately after light Sc and 10 min afterward. The initial cultures were positive for 30% of the subjects; but after 10 min, only 5% of the cultures were positive. In the endodontic treatment group, they found positive cultures in 48 cases in which instruments had extended beyond the apex during endodontic therapy. Immediately after manipulation, 31.2% of the subjects had positive cultures but cultures taken 10 min later were all negative. Roberts et al. (85) cultured 458 blood samples taken from 229 children aged 2 to 16 years. Each sample was taken starting at one of the following times after the extraction of a single tooth: 10 s, 30 s, 60 s, 90 s, 120 s, 180 s, 600 s and continuously over 2.5 min. At 30 s, 56% of the samples were positive. It was the highest proportion in contrast to only 38% of positive samples at 90 s, and 28% at 600 s. Recently, Kinane et al. (48) investigated bacteremia after periodontal procedures. The incidence of bacteremia after US was 13% and it was far below the results of other studies. Authors suggested that this result might be because of the fact that chronic periodontitis patient population used in their study may present a unique patient base whose immune systems are highly primed to cope with periodontal bacteria so that when a bacteremia is induced, it is quickly and efficiently cleared by the patient's reticuloendothelial system. Therefore, it is safe to start taking the blood samples within 2 min after exposure to the bacteremia-inducing factor. On the other hand, bacteremic situation might continue for a period time depending upon the amount of bacteria, the origin of bacteremia, and the property of bacteremia inducing factor, and we believe that the fewer microorganisms present at the origin of the bacteremia the shorter amount of time takes place for the immune system to clear the bacterial presence. Therefore, we arranged the different time points for blood sampling (before and immediately after US, at the 5th min, and at the 10th min from starting of the US) in order to determine not only the effectiveness of mouthwashes in preventing the bacteremia but also the time of which the microorganisms is cleared away from the blood circulation. And, this timing property makes our study original among other studies dealing the bacteremia after US.

Blood volume is one of the factors that can affect the results of bacteremia related studies. If there is a little amount of bacterial presence in the circulation, less volume (1 or 2 ml) blood sampling may not be enough to detect them. Increasing the volume of blood samples is strongly advocated by Loesche (58) and other researchers to increase the chance of isolation of bacteria (82, 90, 104, 118). Tenny et al. (104) studied the bacteremia with different blood volumes. He found that microorganism yield from 7 ml samples 29% greater than from 2 ml samples. In our study, 11 ml of blood samples for each time point was taken 10 ml for SBC and 1 ml for PP method for the detection of the microorganisms as performed in some previous studies (23-25).

The term bacteremia refers to live microorganisms in the bloodstream and culture technique is the only method that grows live bacteria. The sensitivity of blood culture methods is crucial because bacteremia is usually characterized by low concentrations of bacteria in the blood. There are many culturing techniques described in the literature such as Septi-Check blood culture, tryptic soy broth blood culture, Bactec technique, radiometric blood culture system, and SBC (38, 77, 107, 109, 119-121). In our study, we used SBC which is more sensitive, gives accurate results, not time consuming, easy to use, and suitable culture medium for the growth of aerobic and anaerobic bacteria among all other culture medium systems. In our study, we were able to detect both anaerobic and aerobic microorganisms including *S mitis, S. salivarius, S sanguis, Actinomyces,* and *Provetella intermedia* in 21 isolates out of 120 samples with SBC system that was comparable with previous studies (79, 117).

Our results suggest that the reduced incidence of bacteremia is due to the antimicrobial potential of BIO and CHX against oral microorganisms. The AHA recommends rinsing with antiseptic mouthwashes as an adjunct to systemic premedication for high-risk patients (10, 30). In the literature, there are two ways of using chemical antiseptics as an adjunct to the antibiotic prophylaxis. These are either as mouthrinsing agent or subgingival irrigation solution prior to dental treatment. However, according to the AHA's Council on Scientific Affairs, sub-gingival irrigation is not recommended for high-risk patients due to its potential to induce bacteremia, the lack of standard regimen, and insufficient data to indicate the reduction of the incidence of endocarditis (30, 59,

95). Lufthus (59) claimed that sub-gingival irrigation with CHX induce the occurrence of bacteremia by it self. Furthermore, it was stated that it has no effect on the incidence of bacteremia associated with subsequent Sc/Rp. Therefore, we decided to measure the effect of mouthwashes on the incidence of bacteremia as a mouthrinse. We selected BIO, a relatively new an antiseptic solution claiming good antibacterial effect and 0.2% CHX with proven efficacy in decreasing oral bacteria as a positive control (10, 23, 27, 59, 79, 99). Since the use of CHX is not always preferred due to its side effects, we wanted to compare other product, BIO's efficacy with CHX in preventing US related bacteremia. In addition, the finding of studies regarding the use of chemical agents as coolants in the treatment of periodontal diseases would be of interest since its result demonstrated better tissue response in experimental group (CHX) than C group (saline) (29, 102). Therefore, the role of possibly supplementary benefits of antiseptic mouthwashes as coolants to prevent bacteremia during US cannot be excluded. Different from previous studies, to increase the effectiveness of related mouthwash, we further added to the methodology the usage of mouthwash as a coolant in addition to its use as a mouthrinse which was the first time in the literature of the bacteremia related studies. However, in our study, we did not measure the effect of using antiseptic agents as a coolant itself. For this reason, we cannot conclude that this method definitely increase the effect of related antiseptic solutions in preventing the bacteremia. This subject requires further research including larger study population.

In our study, the total number of bacteremias found in the control group was 50% after US. Our results are similar to those detected by Rahn et al. (79) on which the percentage of bacteremia was 52% in control group. But, our results from CHX group, 30% bacteremia were different from their results, 45% bacteremia. The reason for the difference could be due to the usage of CHX as a coolant during US which possibly augmenting the antiseptic effect of CHX. In contrast, in a study conducted by Waki et al. (117), the total number of bacteremias found after Sc/Rp was 18.5% which was lower than our results. Most likely, the difference was due to different bacteriologic technique used in that study. They used Septi-Check system which was less sensitive than our technique, SBC system. Our results from BIO group (40%) were better than control group (50%) in decreasing the incidence of bacteremia and the effectiveness of

BIO was comparable to the effectiveness of CHX (30%). Regarding the duration of the bacteremic status of patients after US, the presented study showed that BIO group was better than CHX group. However statistically it was insignificant. In BIO group, positive results were detected immediately after US only and there was no any positive results detected at the 5th and 10th min from starting of the US. On the other hand, in CHX group, positive results were not only detected immediately after US but also at the 5th and 10th min from starting of the US. It might be assumed that BIO mouthwash might have strong antimicrobial properties that effectively reduces the vitality of the microorganisms so that we could not detect any positive result at later time points (at the 5th and 10th min from starting of the US). This result is promising and requires more research that BIO might replace CHX in preventing or decreasing the incidence of bacteremia during dental procedures. If it is so, we can avoid all complications and side effects related to CHX.

In our study, *Streptococcus* sp accounted for the largest percentage (61.9%) of microorganisms cultured after US. According to a study conducted by Coulter et al. (15), *Streptococci* were most frequently isolated from post-extraction blood as the others findings (18, 20, 37, 103). This is so important since *Streptococcus* sp account for the majority of cases of community acquired IE (8, 17). On the other hand, the prevalence of anaerobic isolates in positive blood culture was lower (23 %) than previously reported (4, 37, 71, 117). This might be due to the absence of deep pockets in patients of our study which creates an unfavorable medium for the growth of anaerobic bacteria. On the other hand, anaerobic microorganisms such as *P. intermedia* were detected in some of the samples. This is not surprising since the detection of such anaerobic bacteria in healthy oral microflora, in saliva and on the surface of the tongue has been reported in previous studies (69, 97).

The results of this study reflect the strict aseptic technique that we followed during collection and microbiologic evaluation of the blood samples in order to reduce the risk of contamination. The blood samples that have been taken pre-operatively had negative results and the organisms identified in the post-operative blood samples were members of the oral microflora. As these organisms are not found on the skin or elsewhere under normal circumstances, their presence in the blood samples is not considered to be due to

contamination during blood withdrawal. We did not detect any skin born microorganisms and only found are of oral origin.

The goal of periodontal therapy is to prevent, arrest, or eliminate disease and restore the periodontium to a state of health which includes comfort, function, and esthetic that can be maintained adequately by both the patient and dental professional. Initial therapy aims to control the bacterial challenge characteristic of gingivitis and periodontitis. Alteration or elimination of putative periodontal pathogens and resolution of inflammation are paramount objective of initial therapy creating an environment conductive to periodontal health and decreasing the likelihood of disease progression.

The clinical outcomes of periodontal treatment modalities are dependent on good plaque control and it is contributed to the observed clinical improvements in non surgical periodontal therapy (114). Our results demonstrated that, regardless of which chemical antiseptic agent used as an adjunct to US, PI and GI values decreased significantly in the 3 groups when compared to baseline values ($p<0.001$). This may be explained by both oral hygiene procedures conducted during the study and the performed Sc/Rp. Moreover, the clinical results of this study demonstrated that the 3 groups had statistically and clinically significant improvement in PPD values ($p<0.001$) at 3 months after US as expected.

8. CONCLUSIONS

Within the limit of this study, we can conclude that US is one of the periodontal treatment procedures that can induce odontogenic bacteremia. Pre-procedural use of BIO mouthwash and CHX resulted in a significant reduction in the incidence of bacteremia associated with US. The results of our study revealed that BIO mouthwash is as effective as CHX in reducing the incidence of bacteremia associated with US. Moreover, BIO might be more effective than CHX in reducing the duration of odontogenic bacteremia induced by US but this requires further investigation.

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MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ
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MAR-YÇ-2006-0106 protokol nolu " Başlangıç periodontal tedavi öncesi ve esnasında kullanılan ağız gargaralarından Klorhex (%0.2 chlorhexidine gluconate) ve Biotene'nin tedavi sırasında meydana gelebilecek bakteriyemi üzerindeki etkisi " isimli projeniz Fakültemiz Araştırma Etik Kurulu tarafından incelenerek onaylanmıştır.

Prof. Dr. Haner DİRESKENELİ
Marmara Üniversitesi Tıp Fakültesi
Araştırma Etik Kurul Başkanı

Sağlık Bilimleri Enstitüsü Müdürlüğü'ne;

Marmara Üniversitesi Sağlık Bilimleri Enstitüsü **Diş Hekimliği Fakültesi Periodontoloji Anabilim Dalı** çerçevesinde yürütülmüş olan bu çalışma aşağıdaki jüri tarafından **Yüksek Lisans tezi** olarak kabul edilmiştir.

İMZA

Tez Danışmanı : Yrd.Doç.Dr.Kemal Naci KÖSE
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ONAY

Yukarıdaki jüri kararı Enstitü Yönetim Kurulu'nun 02 / 11 / 2006 tarih ve ...5... sayılı kararıyla onaylanmıştır.

Prof.Dr.Sevim ROLLAS
Müdür