Original Article

Effect of Postoperative Amoxicillin on Early Bacterial Colonization of Peri-Implant Sulcus: A Randomized Controlled Clinical Trial

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Abstract

Objectives: With side effects of antibiotics taken into consideration, the necessity of antibiotic therapy after simple implant placement procedures is still a subject of debate and the existing literature on this topic is widely controversial. The aim of this study was to assess the effect of postoperative amoxicillin therapy on early colonization of peri-implant sulcus after implant placement.

Materials and Methods: In this randomized controlled clinical trial, 20 patients requiring simple implant placement were randomly allocated to test or control groups and received postoperative amoxicillin or placebo, respectively. Microbiological samples were collected on day 0 and day 7. Mann Whitney and Wilcoxon signed rank tests were utilized to evaluate changes in colony count of identified bacterial species between the test and control groups, and between day 0 and day 7.

Results: The decrease in the number of sensitive facultative species and the increase in the number of resistant anaerobes in amoxicillin group were statistically significant as compared to the placebo group (P=0.025 and P=0.005, respectively). The increase in the number of sensitive anaerobes in the placebo group as compared to amoxicillin group, and the decrease in the number of facultative Gram-positive cocci as compared to the placebo group were statistically significant (P=0.011 and P=0.035, respectively).

Conclusions: Postoperative administration of amoxicillin resulted in an increase in the number of resistant anaerobes and a decrease in the number of sensitive facultative bacteria and facultative Gram-positive cocci, as compared to the placebo, but with no sign/symptom of infection in any group.

Keywords: Dental Implants; Osseointegration; Amoxicillin; Placebos; Infection; Aerobic bacteria, Anaerobic bacteria

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INTRODUCTION

In implant dentistry, adopting appropriate measures to ensure long-term osseointegration is of immense importance, as it can prevent ultimate failure of treatment. Analysis of subgingival plaque by phase-contrast microscopy has suggested that periodontal status of the remaining teeth may affect the composition of peri-implant subgingival flora [1,2]. Although presence of periodontal pathogens does not prove a direct etiologic relationship that would lead to a destructive process, it can reflect the presence of a pathological environment, which makes periodontal tissue susceptible to degradation [3]. The concept of foreign body infections induced by dental implants has attracted extensive scientific attention. These infections are difficult to treat since the causing bacteria reside in organized biofilms and are therefore protected from antibacterial agents [4]. The inflammatory responses observed in peri-implant mucositis or

peri-implantitis may be dependent on certain titanium-associated pathogens or host-related mechanisms. This may explain some specific inflammatory responses observed in peri-implantitis lesions [5]. It has been documented that 30 minutes following implant placement, one-fourth of patients show bacteremia, which could reduce the efficacy of surgery [6].

Moreover, infections developed around biomaterials are very difficult to treat and usually lead to removal of all infected implants. Antibiotics are routinely prescribed for prevention of post-surgical infection after dental implant placement. Although it is critical to reduce the risk of implant failure, it is also important to exercise caution in use of antibiotics to reduce their widely known adverse side effects, ranging from diarrhea to life-threatening allergic reactions. Moreover, emergence of antibiotic-resistant bacteria is another major concern related to widespread use of antibiotics.

A meta-analysis and systematic review published in 2010 recommended short-term antibiotic prophylaxis for implant surgical procedures [7]. However, the results of more recent clinical trials were controversial [8-10].

It would be useful to find the effects of postoperative antibiotic therapy on microbial flora around dental implants. The aim of this clinical trial was to assess the changes in bacterial count in peri-implant sulcus one week after implant placement with and without postoperative amoxicillin therapy.

MATERIALS AND METHODS

Sampling:

This triple blind randomized controlled clinical trial was approved in the Ethics Committee of Tehran University of Medical Sciences (Reference No. 7060-70-02-87) and was in compliance with the ethical principles of the Helsinki Declaration. The study was registered in the Iranian Registry of Clinical Trials (IRCT138706101150N1). A total of 23 patients who were treated in the Dental Implant Department of Dental School, Tehran University of Medical Sciences were enrolled in this study. Patients who met the following criteria were included: 20-60 years of age, partially edentulous, scheduled to receive a maximum number of two implants and adjacent position of implants (when two implants were placed). Patients with the following criteria were excluded: History of recent antibiotic therapy (within the past three months), requiring guided bone regeneration, fixed partial denture in the site of surgery, poor oral hygiene or compliance, periodontal involvement, smokers and patients with systemic diseases. Written informed consent was obtained from all patients who agreed to participate in the study. All patients and the microbiologist were blind to the details of the experiment. Patients were randomly divided into two groups of amoxicillin (test) and placebo (control) using minimization with stratification by age, sex and duration of surgery.

Clinical examination and microbiological sample collection:

Before surgery, phase 1 periodontal therapy, including oral hygiene instruction and scaling and root planing, was performed for all patients. Immediately before surgery, all patients rinsed their mouth with 0.2% chlorhexidine solution for 30 seconds. Then, all implants (Implantium; Dentium, Suwon, Korea) were installed using one-stage protocol. After surgery, each patient was given a random envelope containing three blister packs of capsules (a total of 30 capsules). Patients were asked to regularly brush and floss their teeth except the ones undergone surgery. During the first week after surgery, patients also rinsed 0.2% chlorhexidine solution twice daily.

Postoperative infection was defined as presence of purulent drainage (spontaneous or through incision) or fistula with pain, tenderness, localized swelling, redness, and/or fever. Patients were asked to report the emergence of any symptom to the appointed physician. The sutures

were removed seven days after surgery. During this session, all patients were thoroughly examined by a periodontist for presence of any of the above-mentioned signs/symptoms. The afore-mentioned clinical data were registered in two charts, one for day 0 and the other for day 7. Thirty minutes after implant installation, subgingival plaque samples were collected after proper isolation with cotton rolls. One-third of a #20 paper point was inserted into the sulcus between the implant and tissue in the buccal side, and remained there for 30 seconds. At the same time, a PerioPaper strip was also placed adjacent to the paper point, and after removal of PerioPaper, a paper strip (Periotron®8000; Oraflow Inc., NY, USA) was utilized to determine the volume of gingival crevicular fluid (GCF). The purpose of measuring the volume of GCF was to determine the concentration of bacteria in GCF, as the volume of fluid can affect quantification of colonization. Additional subgingival plaque samples were taken one week after implant placement immediately before removing the sutures in the same manner as described earlier.

Microbiological processing:

One sample was taken from each patient. After sampling, each paper point was placed in sterile Ringer's solution (containing 0.9% sodium chloride, 0.2% calcium chloride, and 0.4% potassium chloride in distilled water) and was transferred to a microbiology laboratory. Immediately after arrival at the lab, pre-reduced broth was used to prepare 10^{-5} serial dilutions of microbial suspension; 20 µL of undiluted sample and each prepared dilution were inoculated onto anaerobic blood agar containing hemin and vitamin K and also onto aerobic blood agar. A sterile spreader was then used to disperse the sample over the surface of solid medium. Resulting cultures were then incubated in suitable conditions i.e. anaerobic blood agar in anaerobic condition (90% N2, 5% CO2 and 5% H2; Anaerocult A Merck Co., Darmstadt, Germany) and aerobic blood agar in normal atmosphere. The plates, wherein the colony count of each species ranged from 30 to 300 colonies, were selected for counting and determining the number of colony forming units (CFUs). Then, according to the dilution ratio, the GCF volume and the volume of suspension used for inoculating the plates, total colony count per milliliter was calculated for different species. In this study, the samples were evaluated for identification of aerobic, anaerobic and facultative bacterial species. Since the surgical area can be contaminated with species with endogenous or exogenous origin, all species with the potential to grow on enriched media were quantitatively evaluated. The anaerobic status of bacteria was determined by oxygen tolerance test. The bacteria cultured on the media were identified by direct microscopic examination based on a set of criteria including Gram staining and metabolism (aerobic, anaerobic or facultative). The results of these tests were used to identify the present bacteria up to species level. Sensitivity or resistance to amoxicillin was evaluated by disc diffusion method conducted in accordance with the guidelines of the National Committee on Clinical Laboratory Standards. To simplify the analyses, bacterial isolates were classified with respect to the following four perspectives: Resistance (resistant or sensitive), metabolism (aerobic, anaerobic or facultative), resistance-metabolism (sensitive aerobic, sensitive anaerobic, sensitive facultative, resistant aerobic, resistant anaerobic or resistant facultative), and morphology-Gram staining-metabolism (Gram-positive aerobic bacillus, Gram-positive anaerobic bacillus, Gram-positive facultative bacillus, Gram-negative aerobic bacillus, Gram-negative anaerobic bacillus, Gram-negative facultative bacillus, Gram-positive aerobic coccus, Gram-positive anaerobic coccus, Gram-positive facultative coccus, Gram-negative aerobic coccus, Gram-negative anaerobic coccus and Gram-negative facultative coccus).

Table 1: Comparison of age, sex and duration of surgery between amoxicillin and placebo groups

Variables	AMX	Placebo	P-value
Age (mean±SD)	48.70 ± 10.88	44.20 ± 15.12	0.178*
Duration of surgery (mean±SD)	26.50 ± 10.01	32.60 ± 11.60	0.949*
Gender (male/female)	4/6	2/8	0.628**
Jaw (Maxilla/mandible)	4/6	5/5	-

SD: Standard deviation, AMX: Amoxicillin group, Placebo: Placebo group, *T-test, **Fisher's exact test

The described microbiological methods were used to evaluate each identified bacteria in each sample with respect to the above-mentioned perspectives. Next, the number of bacterial species in each category defined by the four perspectives was determined. This procedure was performed for both series of samples taken at day 0 and day 7.

It has to be mentioned that in the present study, identified bacterial species in the placebo group were also tested with regard to amoxicillin sensitivity. Hence, "sensitive species" in the control group in this paper means sensitive to amoxicillin.

Statistical analyses:

All data related to different variables were imported into SPSS version 11.5 (SPSS Inc., IL, USA). Nonparametric Mann-Whitney and Wilcoxon signed rank tests were utilized for inter-group comparisons of variables between day 0 and day 7, and intra-group comparisons of variables in the test and control groups between day 0 and day 7, respectively. Statistical significance was defined as $P< 0.05$.

RESULTS

Because of loss to follow-up, we failed to collect day 7 samples of three patients; thereby, this study was finally accomplished with 20 patients (10 patients in each group).

Table 1 shows uniform distribution of age, sex, duration of surgery and position of implants in patients in the two groups.

Bacterial colony count:

In the amoxicillin group, the average count of aerobic, anaerobic and facultative bacteria was 5.0×10^2, 2.91×10^2 and 4.57×10^2 CFUs/mL at day 0, and 5.0×10^1, 8.04×10^2 and 3.0×10^1 CFUs/mL at day 7, respectively. In the placebo group, the average count of aerobic, anaerobic and facultative bacteria was 1.1×10^1, 2.60×10^2 and 8.52×10^2 CFUs/mL at day 0, and 1.0×10^1, 3.78×10^2 and 5.35×10^2 CFUs/mL at day 7, respectively. In the amoxicillin group, the colony counts of aerobic and facultative bacteria at day 7 were significantly less than those at day 0 ($P=0.046$ and $P=0.012$, respectively). However, the change in colony count of anaerobic bacteria from day 0 to day 7 was not statistically significant ($P>0.05$). In the placebo group, the changes in colony count of aerobic, anaerobic and facultative bacteria from day 0 to day 7 were not statistically significant ($P>0.05$). Inter-group analysis of differences in the amount of aerobic, anaerobic and facultative bacterial colonization after one week of antibiotic intake showed no statistically significant change. In other words, the effects of 7-day intake of amoxicillin on bacterial colonization were not significantly different from the effects of placebo.

Number of bacterial species:

Since the bacterial species identified in the samples showed a high degree of variation, bacterial species were classified with respect to four perspectives of resistance, metabolism, resistance-metabolism, and morphology-Gram staining-metabolism.

Intra-group analysis of the number of bacterial species:

Neither the test group nor the placebo group showed any significant change in the number of resistant or sensitive bacterial species from day 0 to day 7.

Table 2: Summary of microbiological findings during the 7-day period (statistically significant results are mentioned)

		Intra-group analysis		Inter-group analysis
		AMX	Placebo	
Total colony count		Aerobic and facultative bacteria decreased	No significant change	No significant difference
Number of bacterial species	Resistance	No significant change	No significant change	No significant difference
	Metabolism	Facultative species decreased	Anaerobic species increased	No significant difference
	Resistance-Metabolism	Sensitive facultative species decreased. Resistant anaerobic species increased.	Sensitive anaerobic species increased.	Sensitive facultative species decreased, while resistant anaerobic species increased in AMX compared to placebo. Sensitive anaerobic species increased in placebo compared to AMX.
	Morphology-Gram staining-Metabolism	Facultative Gram-positive cocci decreased. Anaerobic Gram-negative rods increased.	Anaerobic Gram-negative rods increased.	Facultative Gram-positive cocci decreased in AMX compared to placebo.

AMX: Amoxicillin group, Placebo: Placebo group

In the amoxicillin group, the number of facultative bacterial species at day 7 was significantly less than that at day 0 (P=0.008); in the placebo group, however, this change was not statistically significant (P>0.05).

In the placebo group, the number of anaerobic bacterial species at day 7 was significantly higher than that at day 0 (P=0.002). However, in the amoxicillin group, the change in the number of anaerobic bacterial species between day 0 and day 7 was not statistically significant (P>0.05). In the amoxicillin group, the number of sensitive-facultative bacterial species at day 7 was significantly less than that at day 0 (P=0.010) and the number of resistant-anaerobic bacterial species at day 7 was significantly higher than that at day 0 (P=0.005). In the placebo group, the number of sensitive-anaerobic bacterial species at day 7 was significantly higher than that at day 0 (P=0.023). In the amoxicillin group, the number of facultative Gram-positive cocci significantly decreased, while the number of anaerobic Gram-negative rods increased from day 0 to day 7 (P=0.047). Moreover, in the placebo group, the number of anaerobic Gram-negative rods significantly increased at day 7 compared to day 0 (P=0.008).

Inter-group analysis of the number of bacterial species:

During the 7-day period, changes in the number of resistant and sensitive bacterial species in the amoxicillin group were not significantly different from those in the control group (P>0.05).

The number of sensitive-facultative bacterial species significantly reduced in the amoxicillin group compared to the control group (P=0.010). On the other hand, the number of resistant-anaerobic bacterial species significantly increased in the amoxicillin group compared to the placebo group (P=0.005). Moreover, the number of sensitive-anaerobic bacterial species in the placebo group significantly increased compared to the amoxicillin group (P=0.023).

From the morphology-Gram-staining-metabolism aspect, the number of facultative Gram-positive cocci significantly decreased in the amoxicillin group compared to the placebo group (P=0.035). A summary of the microbiological results is presented in Table 2.

Clinical findings:

None of the patients showed any sign and/or symptom of progressive infection at day 7. One patient in the amoxicillin group and another one in the placebo group showed slight swelling.

The average pain score expressed by patients was 39.0±18.4 in the amoxicillin group and 39.5±15.7 in the placebo group.

DISCUSSION

The objective of this study was to evaluate the effect of amoxicillin, as compared with placebo, on bacterial colonization adjacent to the implant surgical site. The present study failed to recognize significant efficacy of prophylactic systemic administration of amoxicillin for reduction of microbial count around dental implants during the first week after implant placement.

Several studies evaluated the clinical efficacy of prophylactic antibiotic therapy on the outcome of implant surgery [8-18]. However, to the best of our knowledge, this is the first trial that analyzed microbial colonization in the peri-implant site during the first week after implant installation. Based on the results of Frust et al, [19] primary colonization around dental implants takes place 30 minutes after implant insertion. Microbiological sampling in the present study was performed according to Furst et al [19].

Overall, total colony counts significantly decreased from day 0 to day 7 in both groups in our study. This finding could be due to the potential role of chlorhexidine mouthwash as a potent antiseptic agent [17,20]. All patients participated in this study used chlorhexidine mouthwash twice a day (for one week after surgery) and had good oral hygiene. Noteworthily, the decrease in the number of facultative bacterial species from baseline to the 7th day in the amoxicillin group could be explained by the effect of amoxicillin on a wide range of bacterial strains residing in the operated area, as amoxicillin is a broad-spectrum antibiotic with a potent activity against facultative bacteria [18,21].

We found that administration of amoxicillin during the first week after surgery resulted in a rise in the number of anaerobic species. According to the studies conducted by Furst et al, [19] and Kuula et al, [22] anaerobic bacteria play an active role in causing infection, and direct attachment of anaerobic species to the surface of pure titanium can result in spread of bacteria to the tissue surrounding the implant and their subsequent colonization; consequently, infection of the implant site may occur.

The results of the current study demonstrated that amoxicillin intake increased the number of resistant anaerobic bacterial species. On the other hand, in the placebo group, the mutation process leading to emergence of resistant strains did not occur due to no antibiotic intake; instead, sensitive anaerobic bacteria were allowed to grow. This increase can also be due to the presence of necrotic tissues and debris and lack of proper blood circulation in the operated area during the first week after surgery. Another reason might be the wicking behavior of silk sutures and its effect on accumulation of bacteria in the area [23]. Both groups showed an increase in the number of anaerobic Gram-negative rods, which may be due to the fact that in mature plaques, the biofilm ecology usually tends to shift from primary aerobic environment with Gram-positive facultative species to oxygen-deprived environment with dominant Gram-negative anaerobic microorganisms and rods [24]. In addition, the increase in the number of Gram-negative anaerobic rods and decrease in the number of Gram-positive facultative cocci in the amoxicillin group can be attributed to the fact that Gram-negative rods are more likely to develop resistance to amoxicillin than Gram-positive cocci [25]. In a comprehensive study by Mombelli [26] on microbiology of dental implants, it has been reported that successful implants exhibit a higher level of facultative Gram-positive flora, while failed implants exhibit a wider range of anaerobic Gram-negative bacteria.

The results of a study conducted by Sbordone et al, [27] also revealed high prevalence of Gram-

negative anaerobic rods around failed implants (50% of total identified microflora). In contrast, de Moraes Rego et al, [15] showed no significant correlation between bacterial profile and bone loss in peri-implant plaque. In the present study, no sign of infection was detected; thus, it seems that the impact of amoxicillin on reduction of post-surgical complications of systemically healthy patients is insignificant. This finding supports the results of the study by Gynther et al [12]. They found no significant difference between antibiotic group and control (antibiotic-free) group in terms of early or late infection or implant failure. In a study by Esposito et al, [28] the efficacy of prophylactic antibiotics for dental implant placement was evaluated. No statistically significant difference in terms of prosthesis failure, implant failure, postoperative infections or complications was found between the two groups.

The results of the present study were in contrast to those of Dent et al, [11] who assessed the effect of preoperative antibiotics on success of dental implants (up to the second stage), and reported that patients who did not take preoperative antibiotics exhibited a higher rate of implant failure, and preoperative antibiotics significantly increased the success rate of implants. The difference between the results of the present study and those reported by Dent et al, [11] could be due to long-term follow up (four to six months) of implants in their study.

It should be noted that the current study was performed on periodontally healthy patients. Therefore, the results of this trial cannot be extrapolated to periodontally diseased patients. Limited number of targeted bacterial species and small sample size were the limitations of this study. Studies with larger sample sizes and longer follow-ups are needed to verify the results of the present study.

CONCLUSION

Within the limitations of this study, it can be concluded that systemic administration of amoxicillin for one week after simple one-stage implant surgery in periodontally healthy patients was not effective for reduction of total bacterial colony count at the peri-implant site during the first week after surgery, compared to the placebo. Moreover, in this time period, systemic amoxicillin led to an increase in the number of resistant anaerobic species and a decrease in the number of sensitive facultative species, as compared to the placebo.

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