A Pilot Study to Determine the Effectiveness of Different Amoxicillin Regimens in Implant Surgery

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The aim of this study was to attempt to determine the minimum effective regimen of amoxicillin antibiotic prophylaxis for dental implant surgery. One hundred patients were randomly allocated to 4 different antibiotic prophylactic treatment groups. At second-stage surgery, only 2 implants failed in the nonantibiotic group. No statistically significant differences were found in the 4 groups, probably because of the limited number of the samples. Until a study with a larger population may definitely rule on the role of antibiotics in oral implant surgery, in may be prudent for the practitioner to adopt the single preoperative antibiotic dose as the minimal effective regimen.

Key Words: minimum effective dose, antibiotic prophylaxis, oral implant surgery

INTRODUCTION

The use of prophylactic antibiotics before oral surgical procedures in patients at risk for endocarditis or in those who are severely immunocompromised is well established; however, their use in conjunction with implant surgery in healthy patients and their relationship with failure and postoperative complications are still poorly documented. The use of preoperative V-penicillin has been postulated by the Branemark protocol for dental implant surgery.¹ Several other authors²,³ suggested that antibiotic therapy might be important in implant therapy to prevent infections and to preserve the osteointegration process. Most of these studies come from retrospective analysis, multiple nonstandardized operators, and different types of antibiotic agents and regimens, which fail to give any standardized guidelines for antibiotic prophylaxis in this field. More recently, however, it has been observed that a single-day antibiotic regimen may be as effective as a full week of therapy.⁴ Moreover, all controlled studies have found little or no evidence of benefits from prophylactic antibiotics, and there are major adverse risks associated with the use of antibiotics.⁵ A recent Cochrane systematic review failed to provide evidence to recommend or discourage the use of prophylactic systemic antibiotics to prevent complications...
To provide an effective and safe treatment of a certain disease, it is extremely important to identify the dosing range of a pharmaceutical compound. The success of antibiotic therapy depends mainly on achieving a concentration of the pharmaceutical compound that is sufficient to inhibit bacterial growth. The dose of the compound used has to inhibit micro-organism growth without being toxic to human cells. The aim of this study was to evaluate and compare the efficacy of different antibiotic duration in the attempt of founding the minimum effective duration of amoxicillin chemoprophylaxis in dental implant surgery.

**Patients and Methods**

The present study was a prospective, controlled, randomized clinical study. A sample of 100 consecutive patients (42 men and 58 women) who required dental implant rehabilitation in 2 private practices between September 2006 and September 2007 were included in this study.

Patients were not admitted to the study if any of the following criteria were present: (1) history of systemic diseases that would contraindicate surgical treatment, (2) long-term nonsteroidal anti-inflammatory drug therapy, (3) medically necessary antibiotic prophylaxis, (4) history of antibiotic therapy 6 months prior to the study, (5) history of allergic reactions to penicillin or related drugs, (6) pregnancy, (7) failure to sign an informed consent, and (8) unwillingness to return for the follow-up examinations. The patients were randomly allocated—using a computer-generated randomization list—to 4 different groups: (1) single prophylactic antibiotic dose (SPAB) consisting of amoxicillin 2 g 1 hour before surgery, (2) preoperative and postoperative antibiotic treatment (PPAB) consisting of amoxicillin 2 g 1 hour before surgery and 1 g twice a day for 7 days following surgery, (3) postoperative antibiotic coverage (POAB) consisting of amoxicillin 1 g twice a day started after surgery and continued for 1 week after surgery, and (4) no antibiotic treatment (NOAB). Patients were informed about the nature and purpose of the study. Each case was accurately evaluated examining diagnostic casts to assess the interarch relationship, periapical and/or panoramic radiographs, and computerized tomography scan when taken. Following these analyses, all patients underwent preoperative scaling and root planing to provide an oral environment more favorable to wound healing. At the time of surgery, patients were asked to rinse with chlorhexidine gluconate 0.2% solution for 1 minute before each procedure. The clinicians were requested to place the implants according to their routine procedure. Postoperative instructions included cold therapy (ice packs) and assumption of a nonsteroidal anti-inflammatory drug (nimesulide 100 mg twice daily for 3 days). Patients were also instructed to rinse with chlorhexidine gluconate 0.2% twice daily for 15 days following surgery and to refrain from brushing the area of surgery for 2 weeks. The patients were examined at postoperative weeks 1, 2, 4, and 8 for the following clinical parameters: internal and external edema, internal and external erythema, pain, heat, and exudate. Because there is not a gold standard on clinical diagnosis of an infected surgical wound, the number of surgeons involved in the study was limited to 2. The surgeons underwent a period of standardization prior to commencing the investigation. At the second-stage surgery, 3 months after implant placement, implant failure was recorded. Implant failure was defined as mechanical implant removal because of lack of osteointegration. Statistical test analysis was conducted using the commercial package SPSS. Student t test for the difference of group means was applied. A P value of <.05.
was selected as the level of statistical significance with the Bonferroni correction for multiple comparisons.

**Results**

Two centers were involved in this study, with a total of 100 patients. Twenty-five patients were allocated to the SPAB group, 25 to the PPAB group, 25 to the POAB group, and 25 to the NOAB group. All patients were treated according to the allocated interventions, and none dropped out. A total of 148 implants (titanium screw-type external hex) were placed in all groups with the following distribution: 35 in the SPAB group, 36 in the PPAB group, 48 in the POAB group, and 29 in the NOAB group (Table 1). At the 1-, 2-, 4-, and 8-week postoperative visits, infection was not observed in any of the experimental groups. Moreover, no antibiotic adverse events were noted in any group. At second-stage surgery, 3 months after placement, 2 implants were considered failed and were removed in the NOAB group. The overall success rate was 98.65%. The difference between the 4 different groups was not statistically significant ($P < .05$). Table 2 reports the limits of the 99% confidence interval for subgroup differences of averages. Subgroups are antibiotic treatment, sex, and age range; results are obtained assuming different variances of the tested parameter in the 2 groups. The Student test appears to show no significant effect of the treatment, with a very high confidence level (99%). We may further investigate the statistical power of the test, for example, the probability of accepting the hypothesis of the presence of treatment effect if such effect is indeed present. The statistical power of the test is defined as the complement of the probability of a type II error, that is, the error that is made when we accept the null hypothesis when it should have been rejected. The power of the test depends also on the dimension of the sample, and therefore we can identify, for a desired power level, the sample size that would support it. In the case of the data here available, the power of the test is indeed not very high: 15% with confidence at 99% and 35% with confidence at 95%. Further calculations indicate that to have a larger power, the sample size would need to increase significantly: a sample size of at least 80 in each group would indeed lead to a power of 75% with 95% confidence and to a power of 50% with 99% confidence. To obtain 75% of power with 99% confidence, 133 samples in each group would be needed. Such considerations indicate that a larger number of patients need to be analyzed to provide strong statistical evidence of the absence of treatment effect.

**Discussion**

This randomized clinical trial did not reveal any significant differences when comparing the 4 experimental groups. The advantages of prophylactic antibiotics in patients undergoing implant surgery remains controversial. The absence of randomized and controlled clinical studies of antibiotic prophylaxis for dentoalveolar surgery produced conflicting and often equivocal results. Moreover, it should be taken into consideration that endogenous pathogens, such as streptococ-
ci, staphylococci, and anaerobic rods, are the most common cause of wound infection in oral surgical procedures.\textsuperscript{8,9} Penicillin is effective against most pathogens responsible for wound infection, it is less expensive than other antibiotics, and it has less impact on the evolution of resistant bacteria. Nonetheless, the penicillins are the main cause of anaphylactic shock in the United States, accounting for approximately 75\% of the cases and 400 to 800 annual deaths.\textsuperscript{10,11} Of the population, 1\% to 10\% have experienced an allergic reaction to the use of penicillin. In addition, the widespread and unjustified use of antibiotics has caused an increase in bacterial resistance, with potential risks for the efficacy of antimicrobial therapy.\textsuperscript{12,13} It is widely accepted that the most effective and least harmful use of prophylactic antibiotics is a single or short-term, high-dosage regimen, which provides maximal tissue concentration at the time of the surgical intervention.\textsuperscript{13,14} The time of administration of the chemotherapeutic agent has also been thoroughly investigated. Classen and co-workers\textsuperscript{15} reported that a single dose 2 hours before the surgery will produce the lowest rate of postsurgical wound infection. The antibiotic peak therapeutic concentration should be maximal at the time of the incision and at least 3 or 4 times the minimum inhibitory concentration.\textsuperscript{16} Heit and collaborators\textsuperscript{17} suggested a protocol for orthognathic surgery including an antibiotic loading dose 3 to 4 times the therapeutic one, 2 hours before the surgery. A second dose would be required in case the surgical time extends over 120 to 150 minutes. The researchers also reported a reduced effectiveness when establishing antibiotic therapy 3 hours after the end of the surgical intervention. These conclusions are in agreement with Burke’s demonstration that micro-organisms inoculated in wounds are maximally susceptible to chemotherapeutic agents when the drug is already concentrated into the tissue, and the institution of antibiotic therapy 3 hours or more after the inoculation has no detectable effect on the lesion size.\textsuperscript{18} Any use of surgical antibiotic prophylaxis must also take into account the associated adverse effects of antibiotic toxicity and allergy, selection of resistant micro-organisms, superinfections, and effects on microbial ecology in order to achieve a satisfactory risk-benefit ratio.\textsuperscript{19} Heimdahl and Nord\textsuperscript{20} concluded that “at present, it is not justified to use systemic antibiotic prophylaxis in routine dento-alveolar surgery, even if a lower incidence of postoperative infections might be expected.” This is because of the low incidence and self-limiting nature of oral postsurgical infections.

Antibiotic prophylaxis to prevent surgical infections has been proven effective with a reasonable risk-benefit ratio only in clean surgery (open heart surgery, major vascular reconstruction, prosthetic joint surgery), where the risk of infection is remote but its potential consequences grave; in clean contaminated surgery (elective biliary, gastric, or colonic surgery), where the likelihood of infection is great but is seldom fatal; or in artificial prosthesis replacement.\textsuperscript{19} According
to these criteria, implant placement may be one of the few oral surgical procedures requiring routine antibiotic prophylaxis. According to the Branemark protocol, the use of preoperative V-penicillin is advised, and it should be continued 10 days postoperatively.1 Several authors have outlined the importance of antibiotic coverage, whereas others have challenged this conviction. Laskin et al2 stated that “the results showed a significantly higher survival rate at each stage of treatment in patients who had received preoperative antibiotics.” Kashani et al4 recommended a more strict regimen of a 1-day dose of prophylactic antibiotics compared with a full-week prescription. Most of these conclusions come from retrospective analysis, with multiple operators, different antibiotic prescriptions, and different regimens. Despite the widespread use of oral implants in dentistry, we are still lacking a clear guideline on if, when, and how to prescribe antibiotics for this type of surgery. In our study, postoperative infection was not recorded regardless of antibiotic prescription and regimen. We found no statistically significant difference among the different groups regarding complications. Although 2 implant failures were observed in the group of patients without antibiotic treatment, no statistically significant differences can be reported between the different experimental groups. One of the main limitations of this study was the low statistical power to rule out the possibility of a difference between groups. More extensive studies need to be performed to evaluate possible factors affecting the rate of postoperative complications and implant failures in the different experimental groups. From a clinical point of view, since the only 2 failures were in the nonantibiotic group, it would be hard to abandon prophylaxis in dental implant surgery. In that sense, the SPAB dose may be suggested as the minimum effective dose and used in routine implant surgery.

CONCLUSIONS

From the statistical point of view, it could be concluded that prophylactic antibiotics for every implant surgery may not be as necessary as once believed. At the same time, it would be hard to rule out completely the use of antibiotics in oral implant surgery based on these data, especially considering that the only 2 failures were in the NOAB group. Until a study with a larger population may definitely rule on the role of antibiotic in oral implant surgery, in may be prudent for the practitioner to adopt the SPAB as the minimal effective regimen.

ABBREVIATIONS

NOAB: no antibiotic treatment
POAB: postoperative antibiotic coverage
PPAB: postoperative antibiotic treatment
SPAB: single prophylactic antibiotic dose

REFERENCES

8. Lindeboom JA, Baas EM, Kroon FH. Prophylactic single-dose administration of 600mg clindamycin in orthognathic surgery: a prospective randomized study in


