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ORIGINAL ARTICLE

Influence of a single preoperative dose of antibiotics on the early implant failure rate. A randomized clinical trial

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Abstract

Background: The use of a preoperative single dose of antibiotics as routine in conjunction with implant surgery is controversial, in light of the unclear effect on early implant failure rate and risk for development of resistant bacterial strains.

Purpose: This randomized clinical trial compared the early implant failure rates in two different patient cohorts: One group receiving a single dose of preoperative antibiotics (AB group) and one group receiving no antibiotics, prior to implant surgery (noAB group).

Materials and Methods: Patients were referred for treatment at four specialist clinics in the county council of West Sweden, Vastra Gotaland and randomly assigned into one of the two groups. A total of 447 patients received 963 implants were included in the study.

Of these, 223 patients (535 implants) belonged to the AB-group and 224 patients (428 implants) to the noAB-group. Four commercial implant brands were utilized, albeit one system was only represented with four implants.

The outcome was evaluated after 4 months using either a one-stage or two-stage procedure. The surgical procedures were performed by experienced implant surgeons and the surgical protocol for implant placement follows standard. Failure was defined as removal of an implant for any reason. The study outcomes were statistically analyzed to evaluate the differences between the two groups.

Results: Twelve implants failed in 11 patients for the AB group, and 32 implants failed in 29 patients for the noAB group. Preoperative antibiotics, AB group, had significantly ($P < 0.0011$) lower implant failure 2.2% compared to 7.5% in the noAB group analyzed on implant level adjusted for dependence within patients, OR = 0.30, 95% confidence interval (0.14-0.62).

Conclusion: Administration of a single dose of antibiotics in conjunction with implant placement surgery resulted in a statistically significant lower early implant failure rate compared to when no antibiotics were used.

KEYWORDS

antibiotics, dental implant surgery, failures, microbiology, survival rate

1 | INTRODUCTION

The use of dental implants is a well-documented and safe treatment modality for replacement of missing teeth.[1–6] Failures do occur although; either during the early healing phase with implants showing no osseointegration or during the late phase of functional loading with implants loosing osseointegration.[2,7–12] The reasons for early implant failure varies but contamination and infection of the osteotomy site during surgery is one plausable explanation. For instance, it has been shown that dental procedures may induce bacteremia, although for a

short period of time, that is, less than 10 minutes.[13,14] Therefore, prophylactic antibiotic regimens are often used in conjunction with implant placement surgery.[15–21] At the same time, there is an expressed desire within the healthcare communities to decrease the prescription of antibiotics because of the risk of developing resistant microbial strains. Furthermore, the main cause of anaphylactic shocks (approximately 75%) in the United States is the use of penicillin, resulting in between 400 and 800 deaths annually.[22,23] Other unwanted effects of antibiotics are interactions with other medical products leading to nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, candida, and pseudomembranous colitis.[24,25]

The recommendations on the use of prophylactic antibiotics vary. Some authors recommend antibiotic prophylaxis in conjunction with implant surgery only when patients are at risk of infectious endocarditis, patients with reduced host-response, when surgery is performed in infected sites, in cases of extensive and prolonged surgical interventions and when large foreign materials are implanted.[14,26–28] For these purposes, various antibiotic regimens have been used, from a few days preoperative and up to 1-2 weeks postoperative administration. However, most studies have shown no statistically significant differences between 1 week or one dose postoperatively.[29–32] Other authors have recommended one single dose of antibiotics 1 hour prior to implant placement surgery as a routine measure.[32] To the knowledge of the present authors, no randomized clinical trials (RCTs) evaluating the efficacy of prophylactic antibiotics versus no use in conjunction with implant surgery have yet been presented.

The present study aimed to compare the outcome of oral implant treatment due to early failures, by randomizing patients into two groups, one with a single preoperative dose of antibiotic (control) and one without (test).

2 | MATERIALS AND METHODS

2.1 | Study design and ethical considerations

The study was designed as a prospective RCTs including consecutive patients referred for implant treatment at four oral and maxillofacial surgery specialist clinics. The study was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (Dnr: 388-14) and conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki.[33] The study was conducted according to the CONSORT statement (http://consort-statement.org\).

2.2 | Inclusion and exclusion criteria

All patients referred to each clinic for surgical implant treatment and meeting with the inclusion criteria were asked to participate in the study. The inclusion criteria were: (1) need for one or more implants in one or both jaws, (2) no history of antibiotic treatment 1 month prior to implant surgery, (3) being in good general health, and (4) presenting signed informed consent. The exclusion criteria for the study were (1) poor general health (2) previous radiation therapy in the head/neck region, (3) medication with immuno-suppressant drugs and/or bisphosphonates, (4) active chemotherapy, and (5) need of antibiotics prior to and after surgery for medical reasons.

Every other consecutive patient referred to each clinic was allotted to either the antibiotic group (AB-group) or to the no antibiotic group (noAB-group). Selection of study patients was performed by the surgeon at the presurgical evaluation and several surgeons at each clinic were involved in this process. This reduced the risk for individual surgeons to be biased with regard to patients, as every other patient referred to the clinic and not to the specific surgeon was assigned either the AB- or the noAB-group.

2.3 | Treatment and follow-up

The surgical procedures were performed by experienced oral and maxillofacial surgeons following the routines at each clinic and recommendations from the manufacturer of the each implant system.[34–36]

The patients in the AB group received 2 g amoxicillin or, in case of allergy, 600 mg clindamycin 1 hour preoperatively. Placebo was not used in the noAB group. Each clinic followed its standard procedures regarding postoperative analgesics and information/instructions. All patients were seen for a follow-up visit and suture removal after 7-14 days. In case of signs of postoperative infection, which led to prescription of antibiotics, the patient was thus excluded from the study. The duration of healing periods up to abutment connection and/or prosthetic procedures was determined by the surgeon depending on the bone quality and implant stability registered at insertion. Extended healing periods were used in connection with bone grafting procedures. A clinical examination of the implants was performed after the healing period, and in the case of a two-stage surgical procedure, the abutments were applied.

2.4 | Variable

Implant failure was the primary variable and defined as removal of an implant for any reason from implant placement to abutment connection or prosthetic treatment.[37]

2.5 | Statistics

A sample size calculation prior to the study was performed, in which the significance level was set to 0.05 and with a power of 80%.[38] The calculation showed a need for 211 patients per group to identify a 5% difference in survival rate (94% vs 99%) between groups at patient level. A total sample size of 450 patients was estimated to account for a 5% patient dropout rate. Generalized estimating equations modeling with link function logit was used to estimate an overall effect of predictors on implant failures, and adjusted for within patient correlation. Compound symmetry covariance matrix and binomial distribution with logit link function resulting in ORs with 95% confidence interval (CI) as risk estimates were used. All significance tests were two-sided and conducted at 5% significance level. All analyses are done with SAS System for windows version 9.

3 | RESULTS

3.1 | Patients and implants

All patients who fulfilled the inclusion criteria were willing to participate, and a total of 447 patients were consecutively treated in the study (Table 1). Seven patients with 10 implants were in need for postoperative antibiotic treatment. Seven of these implants healed out after 10 days of antibiotics, whereas three were lost and subsequently reoperated. Six of the seven patients belonged to the noAB group. Thus, a number of 447 patients and 963 implants were allocated to the study groups and included in the per protocol analysis.

The AB group consisted of 223 patients (109 males/114 females, mean age 56.0 [SD 17.7] years, range 15-91 years), who received 535 implants. The noAB group consisted of 224 patients (96 males/129 females, mean age 50.8 [SD 18.0] years, range 16-89 years), who received 428 implants (Table 1).

TABLE 1 Baseline characteristic patient level

Variable	Total (*n* = 447)	No antibiotics (*n* = 224)	Antibiotics (*n* = 223)
Gender			
Male	204 (45.6%)	95 (42.4%)	109 (48.9%)
Female	243 (54.4%)	129 (57.6%)	114 (51.1%)
Age	53.4 (18.0) 57.0 (15.0; 91.0)	50.8 (18.0) 54.0 (16.0; 89.0)	56.0 (17.7) 60.0 (15.0; 91.0)
Implant system			
Ankylos	1 (0.2%)	0 (0.0%)	1 (0.4%)
Astra	125 (28.0%)	69 (30.8%)	56 (25.1%)
Nobel	260 (58.2%)	122 (54.5%)	138 (61.9%)
Straumann	61 (13.6%)	33 (14.7%)	28 (12.6%)
Jaw			
Maxilla	269 (60.2%)	144 (64.3%)	125 (56.1%)
Mandible	161 (36.0%)	76 (33.9%)	85 (38.1%)
Both Maxilla and Mandible	17 (3.8%)	4 (1.8%)	13 (5.8%)
Bone grafting			
No	355 (79.4%)	188 (83.9%)	167 (74.9%)
Yes	79 (17.7%)	31 (13.8%)	48 (21.5%)
Both Yes and No	13 (2.9%)	5 (2.2%)	8 (3.6%)
Surgical protocol			
One-stage	113 (25.3%)	53 (23.7%)	60 (26.9%)
Two-stage	328 (73.4%)	169 (75.4%)	159 (71.3%)
Both one and two-stage	6 (1.3%)	2 (0.9%)	4 (1.8%)
Number of implants			
1	210 (47.0%)	122 (54.5%)	88 (39.5%)
2	120 (26.8%)	58 (25.9%)	62 (27.8%)
3	33 (7.4%)	12 (5.4%)	21 (9.4%)
4	44 (9.8%)	17 (7.6%)	27 (12.1%)
5	10 (2.2%)	4 (1.8%)	6 (2.7%)
6	28 (6.3%)	11 (4.9%)	17 (7.6%)
10	2 (0.4%)	0 (0.0%)	2 (0.9%)

For categorical variables *n* (%) is presented.
For continuous variables mean (SD)/median (min; max)/*n* = is presented.

Four implant brands were represented in the study. The overall majority were from Nobel Biocare (611 implants), while the remaining represented Astra Tech (236 implants), Straumann (112 implants), and Ankylos (four implants) (Table 2).

Six hundred implants were placed in 269 maxillae and 363 implants were placed in 161 mandibles. Seventeen patients received implants in both maxilla and mandible (Tables 1 and 2). The majority of the patients (210 patients) received one implant, whereas the maximum number of implants positioned in any patient was 10 (two patients) (Table 1).

A total of 165 implants in 92 patients were inserted in connection with bone grafting procedures (Table 2).

One-stage surgical procedures were made in 113 patients for 233 implants and two-stage procedures in 328 patients for 730 implants. Six patients received both one-stage and two-stage surgical procedure (Tables 1 and 2).

3.2 | Variable outcomes

A total of 40 patients showed implant failure during the study period; 11 in the AB group (4.9%) and 29 in the noAB group (12.9%). Preoperative antibiotics, AB group, had significantly ($P < 0.0011$) lower implant failure 2.2% compared to 7.5% in the noAB group analyzed on implant level adjusted for dependence within patients, OR = 0.30, 95% CI (0.14-0.62) (Table 3).

Forty four implants failed in the 40 patients; 12 in the AB group (2.2%) and 32 in the noAB group (7.5%) (Table 3).

TABLE 2 Baseline characteristics implant level

Variable	Total (*n* = 963)	No antibiotics (*n* = 428)	Antibiotics (*n* = 535)
Implant system			
Ankylos	4 (0.4%)	0 (0.0%)	4 (0.7%)
Astra	236 (24.5%)	104 (24.3%)	132 (24.7%)
Nobel	611 (63.4%)	270 (63.1%)	341 (63.7%)
Straumann	112 (11.6%)	54 (12.6%)	58 (10.8%)
Jaw			
Maxilla	600 (62.3%)	278 (65.0%)	322 (60.2%)
Mandible	363 (37.7%)	150 (35.0%)	213 (39.8%)
Bone grafting			
No	798 (82.9%)	361 (84.3%)	437 (81.7%)
Yes	165 (17.1%)	67 (15.7%)	98 (18.3%)
Surgical protocol			
One-stage	233 (24.2%)	105 (24.5%)	128 (23.9%)
Two-stage	730 (75.8%)	323 (75.5%)	407 (76.1%)
Implant system for implants with bone grafting			
Ankylos	0 (0.0%)	0 (0.0%)	0 (0.0%)
Astra	46 (27.9%)	15 (22.4%)	31 (31.6%)
Nobel	109 (66.1%)	42 (62.7%)	67 (68.4%)
Straumann	10 (6.1%)	10 (14.9%)	0 (0.0%)
More than one system	0 (0.0%)	0 (0.0%)	0 (0.0%)

For categorical variables *n* (%) is presented.

4 | DISCUSSION

The tradition at all participating centers has been to utilize administration of preoperative antibiotics for 8-10 days when treating patients afflicted with immuno-deficiencies, patients exposed to therapeutic radiation, cytotoxic drugs, bisphosphonates, immune-suppressive medication, but also when executing more advanced maxillofacial surgeries. These patient categories were excluded in the current study. However, when referring to implant placement in apparently healthy individuals the performing surgeons have either provided their patients with one preoperative dose of antibiotics or nothing at all. There is no obvious consensus and no real knowledge of what is needed to avoid infections/implant failures. The present RCT evaluated the use of a single dose of antibiotics 1 hour prior to implant surgery as compared to no antibiotics, and the decision was thus to refrain from using placebo. It was shown that prophylactic antibiotics had a marked and statistically significant positive effect on early implant failure rate on both patient (4.9% vs 12.9%, $P = 0.0045$) and implant (2.2% vs 7.5%, $P = 0.0011$) levels (Table 3). Odds-ratio calculations showed a 3-4 times (3.38 odds-ratio at 95% CI, respectively) higher risk for failure without antibiotics. This is in line with a previous study by Dent et al,[39] who found the risk for implant failure to be two to three times higher if no preoperative antibiotics were given. However, other studies have reported no effects of presurgical administration of antibiotics.[40,41] A possible reason could be that, those studies involved fewer patients/implants than the present one and thus not able to show any differences between the groups.

The present paper comprised 963 implants, inserted in 447 patients. The studied patient material was divided into subgroups to describe the treatment variables, such as implant system used, jaw type, the need for augmentation procedures, the surgical protocol (ie, one- or two-stage surgeries), and the number of implants placed per patients. Some of these variables have been shown to have an impact on treatment outcomes, that is, traditionally more implant failures are reported for maxillae versus mandibles, more failures concerning grafting procedures, and more failures may be anticipated with one-stage surgery and early loading in consecutive patient materials.[42–44] This also holds in the present study when ignoring antibiotics/no antibiotics and just comparing pooled groups with grafting versus no grafting and one-stage versus two-stage surgery. When comparing implants in maxillae versus in mandibles, the opposite was found, which is a rather odd finding. One plausible reason although may be the high percentage of one-stage surgeries in mandibles.

The effect of antibiotics was estimated for each subgroup of treatment. Variables and analyses of data were performed to identify potential confounding variables, albeit the present study setup was not optimal for such a procedure. No signs of confounding was possible to find as the complete 95% CI of the overall effect of

TABLE 3 Failure rates for antibiotics and no antibiotics groups, total and by sensitivity subgroups

Variable	Antibiotics/no antibiotics	Number of implants	Failure rate *n* (%)	Odds-ratio (95% CI)	*P*-value*
Overall	No antibiotics	428	32 (7.5%)		
	Antibiotics	535	12 (2.2%)	0.30 (0.14-0.62)	0.0011
Sensitivity subgroup analysis					
Implant system					
Astra Tech	No antibiotics	104	12 (11.5%)		
	Antibiotics	132	4 (3.0%)	0.30 (0.08-1.16)	0.0803
Nobel Biocare	No antibiotics	270	19 (7.0%)		
	Antibiotics	341	7 (2.1%)	0.28 (0.11-0.68)	0.0055
Staumann	No antibiotics	54	1 (1.9%)		
	Antibiotics	58	1 (1.7%)	0.72 (0.05-10.32)	0.8095
Jaw					
Maxilla	No antibiotics	278	19 (6.8%)		
	Antibiotics	322	6 (1.9%)	0.27 (0.10-0.70)	0.0073
Mandible	No antibiotics	150	13 (8.7%)		
	Antibiotics	213	6 (2.8%)	0.31 (0.11-0.83)	0.0195
Bone grafting					
No (=0)	No antibiotics	361	26 (7.2%)		
	Antibiotics	437	9 (2.1%)	0.29 (0.12-0.67)	0.0041
Yes (=1)	No antibiotics	67	6 (9.0%)		
	Antibiotics	98	3 (3.1%)	0.32 (0.08-1.30)	0.1115
Surgical protocol					
One-stage	No antibiotics	105	10 (9.5%)		
	Antibiotics	128	2 (1.6%)	0.15 (0.03-0.75)	0.0209
Two-stage	No antibiotics	323	22 (6.8%)		
	Antibiotics	407	10 (2.5%)	0.36 (0.16-0.82)	0.0148

Odds ratios with 95% confidence intervals and *P*-values are given.
*Generalized estimating equation (GEE) models have been used as they allow for adjustment of within-individual correlation.

antibiotics was shown to lie within all individual 95% CI's for the subgroups.

It is concluded that administration of a single dose of antibiotics in conjunction with implant placement surgery results in a statistically significant lower early implant failure rate on both implant and patient levels compared to when no antibiotics are used.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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