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Efficacy of prophylactic antibiotics for dental implants: a multicentre placebo-controlled randomised clinical trial

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Key words *amoxicillin, antibiotic prophylaxis, dental implants, multicentre randomised placebo-controlled clinical trial*

Purpose: To evaluate the efficacy of prophylactic antibiotics for dental implant placement.
Materials and methods: Twelve Italian private practices agreed to participate in this trial, each centre providing 30 patients. One hour prior to implant placement, patients were randomised, for consumption orally of 2 g amoxicillin or identical placebo tablets. Patients needing bone augmentation procedures were not included. Outcome measures were prosthesis and implant failures, adverse events and post-operative biological complications. Patients were seen 1 week, 2 weeks and 4 months post-operatively.
Results: One centre did not deliver any data and 14 patients had to be excluded from the trial for various reasons. One hundred and fifty-eight patients were evaluated in each group and none dropped out at 4 months. Two prostheses and two implants failed in the antibiotics group, compared with four prostheses and nine implants in the placebo group. There were no statistically significant differences for prosthesis failures, implant losses, complications and side effects.
Conclusions: No statistically significant differences were observed. However, four times more patients in the placebo group experienced implant failures than in the antibiotic group, and this requires further investigation.

■ Introduction

Dental implants are widely used for replacing missing teeth. Despite the high success rates published in the literature, implant failures do occur[1]. It is believed that a certain number of early dental implant losses are due to bacterial contamination at implant insertion[2]. It is known that infections around biomaterials are very difficult to treat, and almost all infected implants have to be removed sooner or later[2]. The likelihood of an infection around dental implants is influenced by the surgical skill (a traumatic and prolonged surgery is more likely to favour infections) and the degree of asepsis. In general, antibiotic prophylaxis in oral sur-

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gery is only indicated in the following situations: patients at high 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.

In order to minimise infections after dental implant placement, various prophylactic systemic antibiotic regimens have been suggested. Initially, antibiotics were recommended preoperatively and up to 10 days post-operatively, one of the most commonly followed protocols being the oral administration of 2 g of phenoxymethylpenicillin (penicillin-V) about 1 hour preoperatively and then 2 g twice a day for 10 days[3]. More recent protocols recommended short-term prophylaxis: 2 g of penicillin-V (or amoxicillin or co-amoxiclav) administered per os, 1 hour prior to surgery and 500 mg of penicillin-V four times a day for 1 day[4].

While it is important to minimise risk of implant failures, it is sensible to minimise the use of antibiotics, since adverse events may occur. Complications most commonly associated with the use of antibiotics range from diarrhoea to life-threatening allergic reactions. Another major concern associated with the widespread use of antibiotics is the selection of antibiotic-resistant bacteria. The use of antibiotics in implant dentistry is controversial, and some controlled clinical trials yielded contradictory results[5–8]. A Cochrane systematic review concluded that there is not appropriate scientific evidence to recommend or discourage the use of prophylactic systemic antibiotics to prevent complications and failures of dental implants[9]. It was also stressed that randomised controlled clinical trials (RCTs) were needed in order to solve the matter, and that large, double-blind, placebo-controlled RCTs assessing whether the use of a single dose of 2 g of amoxicillin 1 hour before implant placement decreases post-operative complications and implant failures could be an appropriate starting point. Therefore, it would be useful to know whether prophylactic antibiotics are effective in reducing post-operative infections and failures of dental implants.

The most recent recommendations by the American Heart Association for the prevention of endocarditis suggested that it is reasonable to use a single dose of 2 g of amoxicillin 30 to 60 minutes before the intervention in patients at high risk for endocarditis (such as those with prosthetic cardiac valves, previous infective endocarditis, unrepaired cyanotic congenital heart disease, completely repaired congenital heart defect with prosthetic material during the first 6 months after the procedure, and cardiac transplantation recipients who develop cardiac valvulopathy), a second dose being not necessary. For individuals allergic to penicillins, 600 mg of clindamycin can be administered instead 30 to 60 minutes prior to the procedure[10].

The aim of the present RCT was to compare the efficacy of 2 g amoxicillin per os with identical placebo tablets taken 1 hour prior to implant placement. The null hypothesis was that there is no difference in the proportion of prostheses that could be placed, early implant failures, post-operative infections and adverse events, between patients receiving prophylactic antibiotics and those receiving a placebo, against the alternative hypothesis of a difference. The present article is reported according to the CONSORT statement for improving the quality of reports of randomised trials (http://www.consort-statement.org/).

■ Materials and methods

Any patient who underwent dental implant placement from September 2006 was eligible for inclusion in this trial. They were not admitted in the study if any of the following exclusion criteria were present:

- at risk of bacterial endocarditis (as decided by the treating cardiologist)
- having implanted biomaterials in the body (hip or knee prostheses, etc.)
- immunosuppressed or immunocompromised
- affected by controlled diabetes and uncontrolled diabetes
- received radiotherapy to the head and neck area
- need for augmentation procedure concomitant with implant placement
- allergic to penicillins
- presence of chronic/acute infections in the vicinity of the planned implant sites
- already under antibiotic treatment for any other reasons
- treated or under treatment with intravenous amino-bisphosphonates
- pregnant and lactating

- enrolled in other clinical studies, whose interventions could interfere with the present trial
- less than 18 years old or not able to sign an informed consent form
- already included once in the present study.

Patients were grouped into three groups according to their declarations: non-smokers, light smokers (up to 10 cigarettes per day) and heavy smokers (more than 10 cigarettes per day).

All patients received thorough explanations and signed a written informed consent form prior to enrolment in the trial. Patients were recruited in Italian private dental clinics with extensive experience in implant treatment. One week prior to implant placement all patients underwent at least one session of oral hygiene instructions and professionally delivered debridement when required. One hour prior to implant placement, patients were randomised into two groups. They received and consumed either 2 g of amoxicillin orally (two tablets of 1 g) or two identical placebo tablets.

Operators were allowed to place and restore the implants according to their routine procedures, so the choice of the implant placement procedure (flapless, immediate implants, conventional approach, etc.), implant type, diameter, length, healing period (immediate, early or conventional loading), and type of restoration was left to the individual operators. Operators had to record the duration of intervention in minutes (from the incision of the mucosa to the last suture or delivery of the healing screw/abutment). Post-operative antibiotics were not allowed; however, if the operator deemed it necessary to prescribe post-operative antibiotics, the reason was recorded, and the patient was retained in the trial. Post-operative chlorhexidine mouthwash 0.2% for 1 minute twice a day for at least 1 week was prescribed to all patients.

Outcome measures were:

- Prosthesis failure: prostheses that could not be placed or prosthesis failure if secondary to implant failures.
- Implant failure: implant mobility of each implant measured manually and/or any infection dictating implant removal. Implant stability of individual implants was tested 4 months after placement by manually tightening the implant abutment with a torque of 28 Ncm (or value depending on the implant system) with a manual wrench.
- Any biological complications such as wound dehiscence, suppuration, fistula, abscess, osteomyelitis, etc.
- Any post-operative adverse events such as erythema multiforme, urticaria, nausea, vomiting, diarrhoea, etc.

These outcomes were recorded at 1 week, 2 weeks and 4 months after implant placement. All assessments were made by the treating dentists, who remained unaware of group allocation for the entire duration of the study.

The sample size was calculated based on the number of patients having at least one early implant failure. A two-group continuity corrected chi-square test with a 0.050 two-sided significance level will have 85% power to detect the difference between a proportion of 0.150 and a proportion of 0.020 (odds ratio of 0.116) when the sample size in each group is 96. However, it was planned to include 180 patients per group to compensate for possible exclusions and drop-outs. Twelve centres agreed to participate in this trial. Each centre had to recruit 30 patients: 15 randomised to the active and 15 to the placebo tablet.

Twelve computer-generated restricted randomisation lists with equal groups of participants were made. Only one of the investigators (ME), not involved in the selection and treatment of the patients, was aware of the randomisation sequence and had access to the randomisation lists stored in his password-protected portable computer. The randomised codes (1 or 2) were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially 1 hour prior to implant placement and patients consumed 2 tablets taken from identical white plastic containers labelled with the same code of the envelopes (1 or 2), containing the antibiotic or identical placebo tablets. Therefore treatment allocation was concealed to the investigators in charge of enrolling and treating the patients, and both patients and operators/outcome assessors were blinded to the tested intervention. Also, the statistician (Prof Helen Worthington) was kept blind and performed all analyses without knowing to which group the patients were allocated.

All data analysis was carried out according to a pre-established analysis plan. The patient was the statisti-

cal unit of the analyses. Differences in the proportion of prosthesis and implant failures, post-operative complications and adverse events were compared between the groups using Fisher's exact probability test. All statistical comparisons were conducted at the 0.05-level of significance. Subgroup analyses were planned to investigate the possible influence of various factors on implant failures, including duration of the procedure, number of implants placed, smokers, and treating centres, but there were too few failures to undertake them.

Results

Twelve centres agreed to participate, but one centre did not deliver any data. Three hundred and thirty patients were enrolled, randomised and treated at the 11 centres, but 14 patients (seven from each group) had to be excluded from the analysis (Fig 1) when checking data without knowing group allocation and the outcome of treatment. Reasons for exclusions were: five patients were included twice in the study (only the data of the first intervention were evaluated). For four patients a sinus lift procedure, planned prior to implant placement, was implemented but this was a clear exclusion criteria; implants were not placed in four patients because insufficient bone was found at surgery and the sites were grafted with autogenous bone. Data of one patient were lost at the treating centre and this was only communicated to the trial coordinator at the time of data analysis.

In total, data from 316 patients were evaluated: 158 patients in the antibiotic group and 158 in the placebo group. The following deviations from the operative protocol occurred: in the antibiotic group three patients were treated with guided bone regeneration using resorbable barriers and autogenous bone, two of them received post-operative antibiotics; in the placebo group antibiotics were prescribed by a doctor to one patient because of influenza 2 days after implant placement.

All patients were treated according to the allocated interventions, and none dropped out. Patients were recruited and treated from September 2006 to March 2007. The follow-up focused on the time between implant placement and 4 months after implant placement.

The main baseline characteristics of patients and interventions are presented in Table 1. There were no apparent relevant baseline imbalances between the two groups. The following implant brands were used: Zimmer Dental (Carsbad, CA, USA); XiVE (Dentsply Friadent, Mannheim, Germany); NobelBiocare (Goteborg, Sweden); Intra-lock (Boca Raton, FL, USA); Camlog (Camlog Biotechnologies, Basel, Switzerland); Dyna (Bergen-op-Zoom, The Netherlands); Biomet 3i (Palm Beach, FL, USA); Endopore (Innova-Oraltronix, Toronto, Canada).

Intra-operative complications occurred in two patients of the antibiotics group: in one patient the vestibular bone plate fractured at implant insertion and was treated with autogenous bone and a resorbable barrier without giving post-operative antibiotics. In another patient the pilot drill broke into the implant site. It was removed and an implant with a diameter larger than originally planned was placed. No relevant complication occurred in the placebo group.

Four months after implant placement, four prostheses could not be placed or failed in the placebo group versus two in the antibiotic group. The difference was not statistically significant ($P = 0.684$; Table 2).

Four months after implant placement, nine implants failed in eight patients in the placebo group versus two implants in two patients in the antibiotic group (Table 3). The difference was not statistically significant ($P = 0.104$; Table 2).

One week after implant placement, one adverse event occurred in the placebo group (itching for 1 day) and one in the antibiotic group (diarrhoea and somnolence). The difference was not statistically significant ($P = 1$; Table 2).

One week after implant placement, two biological complications occurred in the placebo group and four in the antibiotic group (Table 3). The difference was not statistically different ($P = 0.684$; Table 2).

Two weeks after implant placement, one biological complication occurred in the placebo group and one in the antibiotic group (Table 3). The difference was not statistically different ($P = 1$; Table 2).

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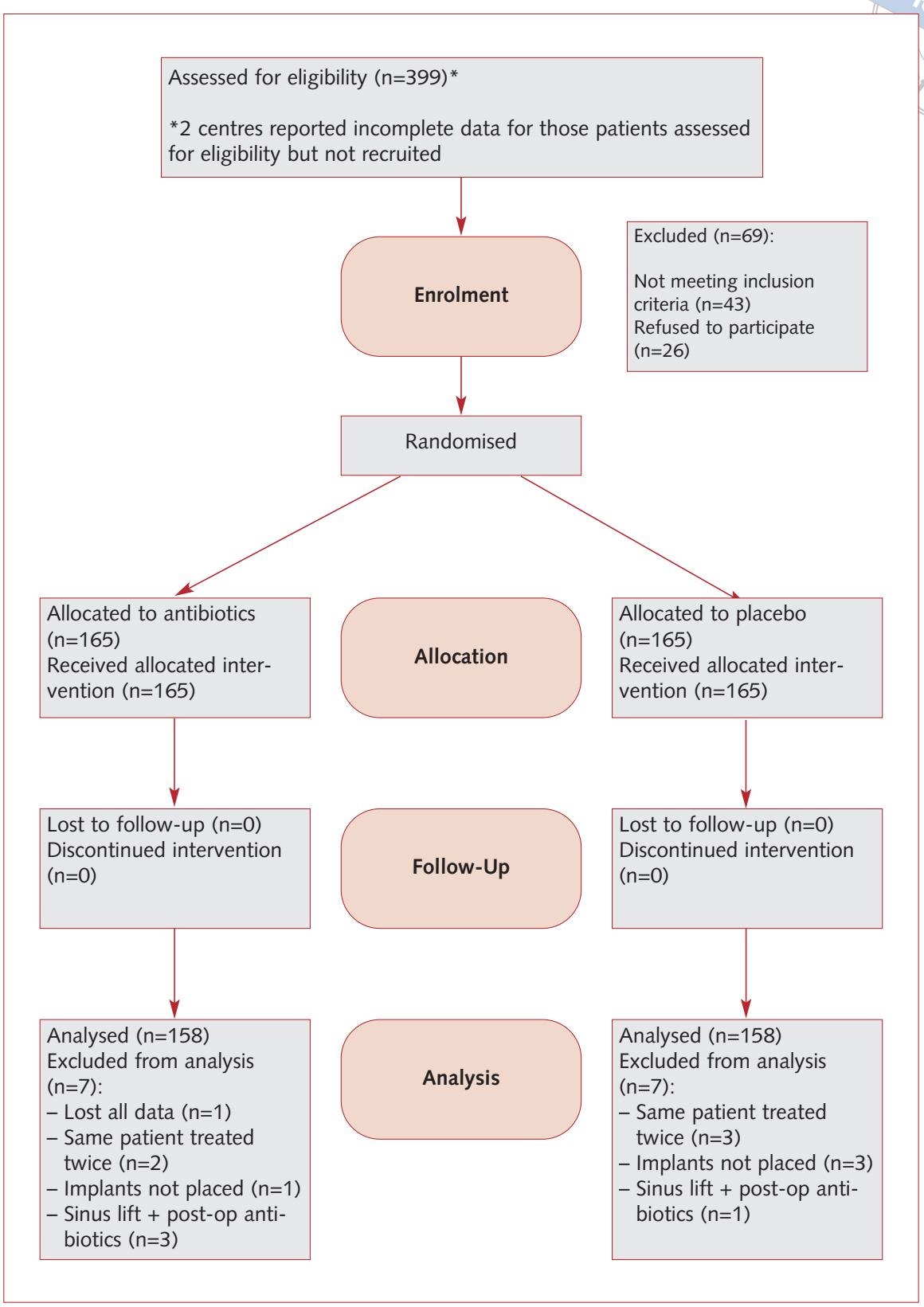

Fig 1 The Consort explanatory flowchart.

Table 1 Characteristics of patients and interventions between the two groups.

	Amoxicillin n = 158	Placebo n = 158
Females	78 (49.4%)	96 (60.8%)
Mean age at implant insertion (range)	47.8 (18–78)	47.9 (19–76)
Non-smokers	99 (62.7%)	108 (68.4%)
Smoking up to 10 cigarettes/day	36 (22.8%)	28 (17.7%)
Smoking more than 10 cigarettes/day	23 (14.6%)	22 (13.9%)
Duration of the intervention in minutes (range)	27 (3–130)	26.5 (4–125)
Total number of inserted implants	341	355
Implants inserted in fresh extraction sockets	62	74
Took post-operative antibiotics	2 (1.3%)	1 (0.6%)
Intra-operative complications	2 (1.3%)	0 (0%)

Table 2 Failures and complications between the two groups.

	Amoxicillin n = 158	Placebo n = 158	*P* values*
Patients who had a prosthesis failure	2 (1.3%)	4 (2.5%)	0.684
Patients who had implant failures	2 (1.3%)	8 (5.1%)	0.104
Patients who had adverse events at 1 week	1 (0.6%)	1 (0.6%)	1
Patients who had complications at 1 week	4 (2.5%)	2 (1.3%)	0.684
Patients who had complications at 2 weeks	1 (0.6%)	1 (0.6%)	1
Patients who had complications at 4 months	2 (1.3%)	1 (0.6%)	0.623

**Fisher's exact test, exact significance 2-sided.*

Table 3 Description of biological complications and implant failures per study group.

	Amoxicillin n = 158	Placebo n = 158
Complications at 1 week	4 flap dehiscence (1 over a resorbable barrier despite post-op antibiotics)	2 flap dehiscence
Complications at 2 weeks	1 flap dehiscence over a resorbable barrier already present at 1 week	1 peri-implant mucositis favoured by the unscrewing of the provisional crown
Complications at 4 weeks	2 peri-implantitis	1 infection signs (mobile implant)
Failures at 4 months	2 mobile implants (1 provoking pain hardly controlled by pain killers)	2 unstable implants (1 placed flapless) immediately replaced by a larger diameter ones 1 spinning implant in a maxilla fully reconstructed with iliac crest graft 1 mobile implant with infection signs 1 implant unscrewed at 2 months when removing the healing screw 4 mobile implants in 3 patients holding mandibular overdentures, 1 immediately loaded

Table 4 Distribution of exclusions, adverse events, biological complications, and implant and prosthetic failures among study centres.

Centre location	Exclusions		Adverse events		Complications		Implant failures		Prosthetic failures	
	A	P	A	P	A	P	A	P	A	P
Pavia	0	0	0	0	0	0	0	1	0	0
Caronno Pertusella	0	0	0	0	0	1	0	0	0	0
Verona	2	2	0	0	2	1	0	3	0	0
Bologna	1	1	0	0	0	0	0	0	0	0
Modena	0	0	0	0	0	0	1	0	1	0
Magenta	0	0	1	1	0	1	0	0	0	0
Cava dei Tirreni	0	0	0	0	1	0	0	1	0	1
Pavia	0	0	0	0	2	0	0	0	0	0
Bolzano	1	3	0	0	0	0	0	0	0	0
Desenzano sul Garda	3	1	0	0	0	0	0	4	0	3
Alessandria	0	0	0	0	1	1	1	0	1	0
Totals	7	7	1	1	6	4	2	9	2	4

A, antibiotic group;
P, placebo group

rence was not statistically significant (P = 0.623; Table 2). The distribution of exclusions, adverse events, complications, implant and prosthetic failures among the different centres is presented in Table 4.

Discussion

This trial was not able to disclose any statistically significant differences when comparing patients who consumed 2 g of preoperative amoxicillin versus 2 g of placebo one hour prior to placement of dental implants. However, the most striking finding is that 4 times more patients experienced early implant losses in the placebo group than patients who received prophylactic antibiotics (8 versus 2 patients, P = 0.104). The interpretation of these findings is difficult. There are two possible explanations: either the sample size was still insufficient to detect a statistically significant difference, or there is not a difference and the perceived difference was only due to chance. The only way to provide a final answer to this disputed clinical question is to conduct another similar trial.

The main limitation of the present trial is that data of 14 patients were not useable or lost. This problem might be partly explained by the fact that many centres were experiencing their first clinical trial and were eager to include rapidly the agreed number of patients. Apart from this problem, no major flaws in the study design and conduct are perceived. The study was conducted using placebo tablets identical to the antibiotics tablets, and produced by the same manufacturer, which allowed the patients and investigators to be blinded for the entire duration of the trial. Ideally, independent outcome assessors should have been used, but there were not the financial resources to undertake this. The trial was not sponsored, although the antibiotics and placebo were generously donated by a drug company manufacturing generic drugs that was not

involved in the design of the study, in the data evaluation or in commenting on the manuscript.

When comparing the present findings with other studies on the same subject, it is difficult to reach additional reliable conclusions. The first study on this subject[5] evaluated implant success at abutment connection (4 to 6 months after implant placement). It compared various dosages and various antibiotics given preoperatively and post-operatively, in most of the cases, versus no antibiotics or antibiotics given with an insufficient dosage in an unknown number of patients (2641 implants). Significantly fewer failures occurred in the antibiotic group (1.5% versus 4%). The study was updated by a second publication[7] that presented data with a follow-up of 3 years after loading. There were 387 patients (1743 implants) in the antibiotic groups and 315 patients (1247 implants) in the control group. The results suggested fewer failures when antibiotics were used (4.6% versus 10%). This multicentre trial was initially described as a RCT[5] but in reality dentists were free to choose when to give or not give antibiotics, which antibiotics to give and which dosage to use. In addition, there was no blind assessment and patients were not considered the statistical unit of the analysis, so the possible clustering of failures was not taken into account.

In a retrospective controlled clinical study[6], 147 patients (790 implants) who received 1 g of phenoxymethylpenicillin 1 hour preoperatively and 1 g every 8 hours post-operatively for 10 days were compared with 132 patients (664 implants) who did not receive any antibiotics. Both groups were treated at the same centre but at different time points (antibiotic group, between 1980 and 1985; no antibiotic group, between 1991 and 1995). No differences in implant survival rates were reported.

In another prospective multicentre controlled clinical study[8], a single preoperative dose of penicillin G or V (1,000,000 units) or 600 mg of clindamycin was compared with an identical preoperative dose plus 300 mg penicillin V orally 4 times a day, or in case of penicillin allergy, 150 mg clindamycin orally 3 times a day, for 7 days. A single dose was given to 125 patients (445 implants), whereas long-term prophylactic antibiotics were given to 90 patients (302 implants). Biological complications only were evaluated at 1 week, 2 weeks and just before abutment connection. There were no differences for biological complications: three wound dehiscences occurred in each group, one developing an infection in the long-term group. The authors concluded that long-tem prophylactic antibiotic use was of no advantage or benefit over a single dose; however, what should have been the primary outcome measure, i.e. implant failure, was not evaluated.

More interesting are the findings of a pilot placebo-controlled RCT[11] comparing a preoperative single-dose of 2 g penicillin pheneticillin with a placebo in 20 patients undergoing intraoral buccal onlay graft covered with resorbable barriers to allow implant placement (the implants were not placed in the study). Two patients developed an infection at both the receptor and donor sites; two patients developed a wound infection at the receptor site; and one patient developed an infection at the donor site only. All of these patients (50%) were in the placebo group. No infections were observed in the antibiotic group. It could be concluded that there was a statistically significant increased risk of having an infectious complication after bone augmentation with resorbable barriers without antibiotic prophylaxis.

Finally, one double-blinded RCT[12] compared 2 g penicillin pheneticillin versus 600 mg of clindamycin as single-dose in patients treated with block-shaped bone graft harvested from the mandibular ramus and covered by resorbable barriers (the implants were not placed in the study). Seventy-five patients were included in each group and the presence of infection was assessed weekly for 8 weeks. No statistically significant differences were observed for post-operative infection (three infections at the donor site of each group). The findings of this trial suggest that both penicillins and clindamycin are effective in reducing infection at augmented sites. No side effects related to the single administration of antibiotics were reported.

The present study was conducted at 11 busy Italian private dental practices experienced in rehabilitating patients with implant-supported prostheses. Success rates were high on average, with only about 3% of the patients experiencing implant failures 4 months after implant placement. The investigators were allowed to treat patients according to their routine procedures, which could be different between centres and could include flapless implant placement, immediate implantation, immediate and early loading procedures, implantation in previously augmented sites, etc. Various implant systems were used, although

the majority of implants were manufactured by Zimmer. The inclusion criteria were not strict, therefore the present results can be generalised with confidence to similar settings.

Conclusions

There were no statistically significant differences for failures and complications when using a single administration of prophylactic antibiotics or a placebo 1 hour prior to implant placement in patients not requiring bone augmentation procedures. However, four times more patients experienced early implant losses in the placebo group than patients who received prophylactic antibiotics (8 versus 2 patients, $P = 0.104$). It is possible that the present trial was underpowered to detect a statistically significant difference; therefore, a further trial is appropriate. No major complications linked with the use of antibiotics occurred. With the lack of definitive evidence, it might be advisable to routinely administer prophylactic antibiotics to patients undergoing dental implant placement.

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