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**Effectiveness of prophylactic antibiotics at placement of dental implants: a pragmatic multicentre placebo-controlled randomised clinical trial**

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

**Purpose:** To evaluate the efficacy of prophylactic antibiotics for dental implant placement.

**Materials and methods:** Thirteen dentists working in private practices agreed to participate in this trial, each centre providing 50 patients. One hour prior to implant placement patients were randomised to assume orally 2 g amoxicillin or identical placebo tablets. Patients needing bone augmentation at implant placement were not included. Outcome measures were prosthesis and implant failures, adverse events and post-operative complications. Patients were seen 1 week, 2 weeks and 4 months post-operatively.

**Results:** Two centres did not deliver any data, two centres did not manage to include the agreed quota of patients and three patients had to be excluded. Two-hundred and fifty-two patients were evaluated in the antibiotic group and 254 in the placebo group, and none dropped out at 4 months. Four prostheses and seven implants (in five patients) failed in the antibiotics group versus 10 prostheses and 13 implants (in 12 patients) in the placebo group. Eleven complications were reported in the antibiotic group versus 13 (in 12 patients) in the placebo group. No side effects were reported. There were no statistically significant differences for prosthesis failures, implant losses and complications. Patients receiving immediate post-extractive implants had an increased failure risk compared with patients receiving delayed implants (9% versus 2%).

**Conclusions:** No statistically significant differences were observed, although trends clearly favoured the antibiotic group. Immediate post-extractive implants were more likely to fail.

**Introduction**

It is still debated whether early failures of dental implants and post-operative infections can be reduced by antibiotic prophylaxis. While it is important to minimise implant failures, there are concerns associated with the widespread use of antibiotics, since adverse events may occur. Adverse events are usually minor (diarrhoea, erythema multiforme, urticaria, etc.) but life-threatening allergic reactions may occur. In addition there is the risk of selecting antibiotic-resistant bacteria.

A recent Cochrane review on this topic concluded that 2 g of amoxicillin given orally 1 h preoperatively significantly reduces failures of dental implants placed under ordinary conditions. In particular, giv-
The aim of this pragmatic multicentre RCT was to compare the effectiveness of 2 g amoxicillin with identical placebo tablets assumed orally 1 h prior to implant placement. The null hypothesis was that there were no differences in success and complications between patients receiving prophylactic antibiotics, and those receiving a placebo, against the alternative hypothesis of a difference. The present trial is a replication of a previous study and 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 April 2008 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 or not controlled diabetes
- received radiotherapy to the head and neck area
- in need of augmentation procedure concomitant with implant placement
- allergic to penicillins
- presence of chronic/acute infections in the vicinity of the planned implant site(s)
- already under antibiotic treatment for any other reasons
- treated or under treatment with intravenous amino-bisphosphonates
- pregnant or 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
- already included in the present study.

Patients were categorised into three groups according to how they classified themselves:

- non-smokers
- light smokers (up to 10 cigarettes per day)
- heavy smokers (more than 10 cigarettes per day).

All patients received through explanations and signed a written informed consent form prior to be enrolled 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 to receive either 2 g of amoxicillin orally (2 tablets of 1 g) or 2 identical placebo tablets, and received 2 tablets of antibiotics or placebo. Patients rinsed for 1 min prior to implant placement with chlorhexidine mouthwash 0.2%.

Operators were allowed to place and restore the implants according to their routine procedures. Therefore 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 according to an intention-to-treat analysis. Post-operative chlorhexidine mouthwash 0.2% for 1 min twice a day for at least 1 week was prescribed to all patients.

Outcome measures were as follows.

- Prosthesis Failure: prostheses which 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 closer values depending on the implant system), with a manual wrench.

- Any 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 findings of patients experiencing at least one implant failure in a previous identical trial. In the antibiotic group, 1% of patients experienced failures, versus 5% in the placebo group. A two-group continuity corrected chi-square test with a 0.050 two-sided significance level will have 80% power to detect the difference between a proportion of 0.050 and a proportion of 0.010 (odds ratio of 0.192) when the sample size in each group is 333. Thirteen centres agreed to participate in this trial. Each centre had to recruit 50 patients: 25 randomised to the active and 25 to the placebo tablets for a total of 650 patients.

Thirteen computer generated restricted randomisation lists with equal groups of participants were made. Only one of the investigators (Dr Marco Esposito), not involved in the selection and treatment of the patients, was aware of the randomisation sequence and could have 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 h 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 statistical 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. It was originally planned to investigate the possible influence of the following factors on implant failures: duration of the procedure, number of implants placed, smoking habit, and treating centres, however, only two hypotheses were tested. A logistic regression model was fitted to the dependent variable implant failure, which included centre as a factor, to investigate whether there was a centre-effect with antibiotic or not as a factor in the model. A chi-square analysis was used to test the hypothesis whether patients receiving immediate post-extractive implants were more likely to experience implant failures than patients receiving delayed implants. We determined whether the patient received any immediate post-extractive implants and cross-tabulated this with whether the patient had any implant failures.

Results

Thirteen centres agreed to participate, but one centre withdrew from the study, one centre did not deliver any data, one centre gave all the study material to another centre which therefore recruited 100 patients, and two centres managed to recruit only 34 and 25 patients instead of the 50 patients as agreed.

Five-hundred and nine patients were enrolled, randomised and treated at the 10 centres but three patients had to be excluded from the analysis (Fig 1) when checking data without knowing group allocation and the outcome of treatment. Two patients were excluded from the antibiotic group because one patient was included twice in the study (only the data of the first intervention were evaluated), and in one patient it was not possible to place the implant. Data of one patient randomised to the placebo group were lost at the treating centre. One patient was a pipe smoker and he was considered to be equivalent to a patient smoking up to 10 cigarettes per day.
In total, data from 506 patients were evaluated: 252 patients in the antibiotic group and 254 in the placebo group.

Three deviations from the operative protocol occurred in antibiotic group: two patients were given post-operative antibiotics, one because a split-crest procedure was performed and the other because the implant replaced a previously failed post-extractive implant; another patient was an insulin-dependent diabetic who should have not been included in the trial. Nine protocol deviations occurred in the placebo group: five patients were given post-operative antibiotics, four because of long interventions (specifically three for post-extractive single implants) and one for a crestal sinus lift procedure; four non-insulin dependent patients were included (one of these patients had the implant site augmented with a bone substitute and a resorbable barrier because the vestibular bone plate fractured during implant placement). A single centre accounted for 67% of patient exclusions and 50% of the protocol deviations (Table 1).

All patients were treated according to the allocated interventions, and none dropped out. Patients were recruited and treated from April 2008 to November 2009. The follow-up focused on the time between implant placement and 4 months after implant placement.

The main baseline patient and intervention characteristics are presented in Table 2. There were no apparent relevant baseline imbalances between the two groups. Implants of the following implant brands were used: Zimmer Dental, Dentsply Friadent, Nobel Biocare, Intra-Lock, Camlog, Dyna, Biomet 3i, Endopore, Z-system, PF Tecom, Ghimas, Silpo, MegaGen and Geass.
The distribution of exclusions, post-operative complications, implant and prosthetic failures among the different centres is presented in Table 1.

The distribution of intra- and post-operative complications by study group is presented in Tables 2 and 3, respectively. There were no statistically significant differences at any time points for complications. Intra-operative and post-operative complications are described in Table 4. No adverse events were reported.

Four months after implant placement, 10 prostheses could not be placed or failed in the placebo group versus 4 in the antibiotic group. The difference was not statistically different ($P = 0.11$; Table 3).

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**Table 1** Distribution of exclusions, post-operative complications, implant and prosthetic failures between study centres

**Table 2** Patient and intervention characteristics

**Table 3** Distribution of failures and complications between the two groups

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

**One patient experienced two complications: one at 1 week and one at 4 months at the same implant, which failed.
Four months after implant placement, 13 implants in 12 patients failed in the placebo group versus 7 implants in 5 patients in the antibiotic group. The difference at patient level was not statistically different ($P = 0.083$; Table 3). A description of the implant failures is given in Table 5.

The logistic regression model fitted for the dependent variable implant failure including ‘centre’ as an effect in the model found no effect whether antibiotics were given or not ($P = 0.10$), or for centre ($P = 0.97$). The $P$-value for implant failures by patient receiving or not antibiotics was similar to without including ‘centre’ in the model ($P = 0.10$).

The hypothesis that immediate post-extractive implants were more likely to fail was confirmed by the chi-square test (9% failure in immediate group versus 2% failure in delayed group; chi-square 1 df 12.5, $P < 0.001$). There was no evidence that antibiotics helped to reduce failures in patients ($n = 99$) receiving immediate post-extractive implants (chi-square 1 df 0.50, $P = 0.48$).

**Discussion**

The present trial was designed in an identical way to a previous study$^3$ aimed at understanding whether
the administration of 2 g of amoxicillin 1 h prior to placement of dental implants was able to reduce post-operative complications and failures. The previous study failed to show any statistically significant differences but clearly showed trends suggesting that amoxicillin may reduce early implant failures. Therefore it was decided to design an identical trial but with a larger sample size to be able to detect some possible statistically significant differences. The results of the present trial are very similar to those of the previous study. In fact, no statistically significant differences were observed but again trends favoured the administration of antibiotics. More patients experienced early implant losses in the placebo group than patients who received prophylactic antibiotics (12 versus 5 patients, \( P = 0.083 \)). Our interpretation of these findings is that the sample size was again insufficient to show a statistically significant difference. This is supported by the findings of a meta-analysis of four trials, including the present study, presented in a recent Cochrane review, suggesting statistically more implant failures when antibiotic prophylaxis is not used.

The main limitations of the present trial are that the planned sample size could not be obtained and that data of three patients were not usable or lost. Efforts were made to select centres able to fulfil the required sample size. Nevertheless, two centres that

<table>
<thead>
<tr>
<th>Amoxicillin</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>No. of patients = 5</td>
<td>No. of patients = 12</td>
</tr>
<tr>
<td>2 mandibular post-extractive implants lost (position 32 and 42) out of 4 implants for infection, 2 weeks after their placement (patient rehabilitated anyway with a bar-supported overdenture).</td>
<td>1 single post-extractive implant (position 44) painful with apical swelling (infection) 1 week after placement, given amoxicillin 1 g x 2 x 6 days, and lost 1 month after placement.</td>
</tr>
<tr>
<td>Asymptomatic failure of 1 single post-extractive implant (position 22) in site having just experienced an implant failure, given amoxicillin 1 g x 2 x 6 days, and found not integrated 4 months after placement.</td>
<td>Asymptomatic failure of 1 mandibular distal implant supporting an overdenture recorded 4 months after placement, prosthesis remained in function.</td>
</tr>
<tr>
<td>Painful single implant placed without elevating a flap (position 36), lost 2 weeks after loading.</td>
<td>Asymptomatic single implant found to be mobile 4 months after placement.</td>
</tr>
<tr>
<td>Asymptomatic failure of the 2 post-extractive implants (5 implants placed, 2 post-extractive), 2 weeks after placement.</td>
<td>Asymptomatic single implant found to be mobile 4 months after placement.</td>
</tr>
<tr>
<td>Asymptomatic failure of a single implant (position 46), 2 weeks after placement.</td>
<td>Lost 1 post-extractive implant (position 45) out of 2 for infection (pus), 1 week after placement.</td>
</tr>
<tr>
<td>Asymptomatic post-extractive single implant (position 37) found to be mobile 4 months after placement.</td>
<td>Asymptomatic implant out of 2 placed (position 11) found to be mobile 4 months after placement.</td>
</tr>
<tr>
<td>Asymptomatic single implant (position 45) found to be mobile 4 months after placement.</td>
<td>Asymptomatic single implant (position 45) found to be mobile 4 months after placement.</td>
</tr>
<tr>
<td>1 out of 4 implants placed, lost for abscess 4 months after placement. A flap dehiscence occurred 1 week after placement.</td>
<td>2 implants lost 2 weeks after placement for infection (pus, pain and swelling).</td>
</tr>
<tr>
<td>Asymptomatic post-extractive implant (position 45) found mobile at abutment connection 6 months after placement. 2 implants placed.</td>
<td>Asymptomatic implant found mobile at abutment connection 4 months after placement. Two implants placed.</td>
</tr>
</tbody>
</table>

**Table 5** Description of implant failures by study group
participated to the previous trial withdrew during the course of the study without providing any data, and two new centres failed to recruit the required number of patients. It appears that the problem in recruitment in the two new centres was the high number of patients refusing to join the trial, and this might be explained with the geographical locations of the centres and the socio-economic conditions of the patients.

Regarding the data of the three excluded patients, it is highly unlikely that results could have been affected. Apart from these problems, no major flaws in the study design and conduct are perceived. The study was conducted using placebo tablets identical to the antibiotic ones, produced by the same manufacturer. This allowed patients and investigators to be kept blinded for the entire duration of the trial. The study was not sponsored, although the antibiotics and placebo were generously donated by a drug company manufacturing a generic drug; the company 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 the other RCTs testing the same hypothesis, two trials provided very similar results, whereas one trial displayed no trends in favour of antibiotic prophylaxis. Two implant failures occurred in each group, and this trial [present trial or ref 4?] included only patients requiring single implants coated with plasma rich in growth factors, placed bone of medium quality and was grossly underpowered, therefore its findings should be interpreted with caution.

In the present trial, patients requiring any type of bone augmentation were excluded. This decision was taken not to expose patients to unnecessary risks. The rationale for this decision is based on the findings from a pilot study, clearly suggesting the benefit of antibiotic prophylaxis for patients undergoing bone augmentation procedures. In this pilot placebo-controlled RCT, a preoperative single-dose of 2 g penicillin pheneticillin was compared with a placebo in 20 patients undergoing intra-oral buccal onlay graft covered with resorbable barriers to allow implant placement (the implants were not placed in the study). A statistically significant increased risk for infections was found when no antibiotic prophylaxis was given. In fact, 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 infection was observed in the antibiotic group.

The present investigation was designed as a pragmatic trial in order to evaluate the effectiveness of prophylactic antibiotics to prevent complications, and failures of dental implants placed under routine conditions. Operations were conducted in 10 Italian private dental practices having extensive experience with dental implant rehabilitation and high patient volumes to speed-up recruitment. Investigators were allowed to treat patients with the type of implants they used routinely according their preferred procedures, which differed between centres and include flapless implant placement, immediate post-extractive implantation, immediate and early loading procedures, implantation in previously augmented sites, etc. Since the inclusion criteria were broad (only patients presenting potential risks for receiving amoxicillin or not receiving antibiotic coverage were excluded), and the lack of centre-effect (i.e. all centres has similar results), the generalisation of the present findings to similar settings can be made with confidence.

Success rates were on average high, with 3.4% of the patients experiencing implant failures 4 months after implant placement. However, it is interesting to observe that immediate post-extractive implants were more likely to fail. In fact, 9% of the patients who received immediate implants experienced implant failures versus 2% of the patients receiving only delayed implants. Of the 20 failed implants (17 patients), 9 were post-extractive (7 patients) and 4 post-extractive implants (3 patients) showed clinical signs of infection. Our findings confirm the trends observed in a Cochrane systematic review that immediate post-extractive implants may be at higher risk for failure. While clinical research evaluating the exact indications for post-extractive implants is currently ongoing, it might be sensible to test prophylactic strategies to minimise failures caused by infections at post-extractive implants. It might be interesting to evaluate whether a prolonged antibiotic coverage initiated one day prior to implantation could decrease failures of post-extractive implants.
The question of which could be the most effective prophylactic antibiotic in preventing implant failures has still to be answered. However, a double-blinded RCT comparing a single dose of 2 g penicillin phenicillin versus 600 mg of clindamycin in patients augmented with block-shaped graft harvested from the mandibular ramus and covered with resorbable barriers (the implants were not placed in the study) suggested no difference between the two antibiotic types. Seventy-five patients were included in each group and the presence of infection was assessed weekly for 8 weeks. Three infections occurred at the donor site of each group. No side affects were reported.

Conclusions

There were no statistically significant differences for failures and complications when using a single administration of prophylactic antibiotics or a placebo 1 h prior to implant placement in patients not requiring bone augmentation procedures. However, more than the double the number of patients (12 versus 5) experienced early implant losses in the placebo group compared with patients who received 2 g of preoperative amoxicillin. No adverse events were reported. It appears that the present trial was underpowered to detect statistically significant differences, therefore a meta-analysis of similar RCTs or even further trials are required to provide the definitive answer. Based on these preliminary findings, it might be advisable to routinely administer prophylactic antibiotics to patients undergoing routine dental implant placement procedures. Immediate post-extractive implants were more likely to fail than delayed placed implants.

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