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A multicentre placebo-controlled randomised clinical trial of antibiotic prophylaxis for placement of single dental implants

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Purpose: to compare the efficacy and safety of 2 g amoxicillin orally with identical placebo tablets 1 hour before implant placement when placing single implants in bone types II and III.
Material and methods: 12 private dental clinics in Spain agreed to participate in this trial. A total of 105 patients were recruited. Patients were randomised for consumption orally of 2 g amoxicillin or identical placebo tablets. Only patients needing single implants were included. Outcome measures were post-operative infections, adverse events and implant failures. Characteristics of the saprophytic flora were also studied in all patients. Patients were seen 3 days, 10 days, 1 month and 3 months post-operatively.
Results: A total of 105 patients (n = 52 in the amoxicillin group and n = 53 in the placebo group) were evaluated and none were excluded from the study at 3 months. Six post-operative infections occurred and two implants were lost in each group. There were no statistically significant differences for post-operative infection, adverse events, implant failures and the characteristics of saprophytic flora between groups. The use of amoxicillin did not either alter or modify the characteristics of the saprophytic flora nor provoke remarkable side effects.
Conclusions: Antibiotic prophylaxis may not be needed when placing single implants in patients with bone types II and III.

■ Introduction

The use of dental implants for replacing missing teeth is a widely accepted treatment. Recently, survival rates superior to 99.2% have been reported for Biotechnology Institute (BTI) dental implants humidified with plasma rich in growth factors (PRGF), placed in different anatomical locations and using a wide range of procedures[1-3]. Despite the high success rates, implant failures do occur, and some of them are related to bacterial contamination at implant insertion[4].

The use of antibiotics, and especially of antibiotic prophylaxis, in oral implantology is still a matter of

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debate. The purpose of antibiotic prophylaxis in surgery is to prevent infections at the surgical wound by obtaining antibiotic concentrations in blood that prevent bacterial proliferation and spread from the gateway, i.e. the surgical wound. In general, antibiotic prophylaxis is provided to patients with high and moderate risk of endocarditis, with reduced host-immune response, patients with metabolic diseases, patients receiving radiation in areas of the head and neck, in cases of extensive and prolonged surgical procedures, and when large foreign materials are implanted. In addition, there are no standardised protocols for antibiotic prophylaxis in straightforward implant surgeries and those reported usually result in excessive antibiotic prescription for both therapeutic and prophylactic use[5].

A 2003 Cochrane systematic review concluded that there was no reliable scientific evidence to recommend or discourage the use of antibiotic prophylaxis to prevent complications and failures of dental implants[6]. In 2008, this systematic review was updated including two new randomised controlled clinical trials (RCTs)[7,8]. Authors concluded that there were statistically significantly more implant failures when a prophylaxis antibiotic was not used and that antibiotic prophylaxis could prevent 1 patient experiencing implant failures for every 25 patients receiving antibiotics. In addition, it was stressed that new RCTs will be needed to shed light on this and other issues.

In the present RCT, the efficacy and safety of 2 g amoxicillin orally has been compared with identical placebo tablets 1 hour before implant placement of single implants in patients with bone types II and III. The hypothesis was that there was no difference in early implant failures, post-operative infections and complications between patients receiving prophylactic antibiotics and those receiving a placebo. The present article is reported according to the CONSORT statement for improving the quality of reports of randomised trials (http://www.consort-statement.org/).

Material and methods

This randomised clinical trial was multicentre, placebo-controlled, and double-blinded in two parallel groups. The randomised clinical trial was approved by the Basque Country's Ethics Committee and by the Spanish Medicines Control Agency. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration revised in 2008. A total of 240 patients were to be recruited and treated in 12 private dental clinics in Spain, following the Good Clinical Practice guidelines. Twenty patients were to be recruited and treated by each centre. All patients fully understood the scope of the study and signed the informed consent form.

Patient inclusion criteria included: age between 18 and 75 years, requirement for single implant placement, bone quality II or III (determined by high-resolution scans of the mandibles using a computed tomography scanner). The alveolar bone density, measured in Hounsfields (HU), was determined by the BTI Scan® program (BTI, Vitoria, Spain). Bone type III ranged from 400 to 700 HU whereas bone type II ranged from 700 to 1100 HU.

Patients were not admitted in the study if any of the following exclusion criteria were present:

- allergy to beta-lactam antibiotics
- concurrent local or systemic infections requiring antibiotic treatment
- systemic diseases that contraindicate the surgery including cardiovascular diseases, respiratory diseases, haematological and metabolic disorders, bone diseases, collagenosis, immunodeficiencies and renal insufficiency
- received irradiation to the head and neck (>5000 rads).

The randomisation was performed using a random numbers table, assigning each patient to one of two treatment groups (active or placebo). Each of the enrolled patients had a patient number and, according to the randomisation table, was assigned to each treatment group. Both researchers and patients remained blinded to the received treatment group. For this purpose, the tablets corresponding to each patient were included in a package identified only by the study number and the patient code. Researchers had a sealed envelope for each patient to establish the randomly assigned treatment if necessary. The envelope was opened at the end of the study. Only

in those situations in which the clinician observed any side effect was the envelope opened before. Patients were divided into one of the following two groups:

- experimental group: patients received two tablets of 1 g of amoxicillin (2 g) administered orally 1 hour before implant surgery. The tablets contained, apart from the biologically active drug, aspartame, crospovidone and magnesium stearate as excipients.
- control group: patients received two placebo tablets administered orally 1 hour before implant surgery. The placebo tablets contained microcrystalline cellulose and magnesium stearate as excipients.

Patients received, during the days prior to the intervention, appropriate prophylaxis and adequate oral hygiene instructions. Antibiotics and other medications were not allowed 15 days before the surgery. Demographic information, patient's clinical history, smoking, alcohol, previous medication or radiation, previous periodontal disease, parafunctions, and pathological lesions were recorded.

Prior to the intervention, patients had to perform 1 minute rinses with chlorhexidine mouthwash 0.20%. Immediately after finishing the surgery, patients received an intravenous or intramuscular administration of 4 mg of dexamethasone, followed by decreasing doses of oral dexamethasone (starting with 3 mg, 1 tablet of 1 mg/8 hours, at day 1 post-surgery and a progressive decrease during the following 3 days: 1 tablet/12 hours the second day, 1 tablet in the morning of the third day and a half tablet in the morning of the fourth day). Patients were allowed, in case of pain, to use acetaminophen as rescue medication both before and after the intervention (maximum 1 g/8 hours). Administration of metamizol (575 mg, 1 or 2 tablets/8 hours) was also allowed.

Experienced surgeons, following an adequate treatment plan, performed all implant placements, whereas rehabilitations were carried out by experienced prosthodontists. The treatment plan included careful evaluation of the patient's clinical history, a complete radiological evaluation (conventional x-ray and the BTI Scan), elaboration of surgical guides and the preparation of provisional and final prostheses adapted to each patient.

PRGF preparation

Before placement, implants were carefully humidified with liquid PRGF as described elsewhere[9-11]. Peripheral blood (20 to 30 ml) from each patient was taken by venipuncture before surgery and placed directly into 9 ml tubes (BTI blood collecting tubes) which contain 3.8% (wt/vol) sodium citrate as anticoagulant. Liquid PRGF was prepared by centrifugation (PRGF System®, BTI) at 460 × g for 8 minutes at room temperature. The 1 ml plasma fraction was located just above the red cell fraction, not including the buffer coat, was collected and deposited in a glass dish. In order to initiate clotting, PRGF activator (calcium chloride) was added to the liquid PRGF preparation (50 µl PRGF activator per ml of preparation).

Surgical protocol

Operators followed a common surgical protocol to insert and restore the implants[3]. Patients and the corresponding surgical areas were prepared and cleaned conveniently. Regardless of the intervention area, an infiltrative anaesthesia was applied to all patients on both vestibular and lingual sides. Single implants were placed in the maxilla or mandible. A meticulous and atraumatic elevation of the periosteum was carried out in order to leave the cortical bone clean and free of fibrous tissue. All implants were inserted without irrigation using a low-speed drilling procedure (50 rpm)[12]. All patients received BTI dental implants. Implants were humidified with liquid PRGF before installation. Operators were instructed to record the duration of the intervention in minutes. Surgery phase two was conducted at 3 to 4 months after the initial surgery.

The primary outcome variable was the presence of post-operative infections and the secondary outcomes were infection-free time and implant survival. The latter was measured by testing the stability of the implants with Osstell (Osstell, Göteborg, Sweden) 3 months after implant placement. The diagnosis of post-implant infection was carried out using defined clinical criteria which include inflammation, pain, heat, fever and discharge. Presence of infection was recorded at 3 days, 10 days, 1 month and 3 months (final follow-up period) after implant placement. All assessments were made by the treating dentists, who

remained unaware of group allocation for the entire duration of the study. During the initial follow-up visit, a sample of the bacterial flora was taken from the buccal mucosa. Standardised samples were taken using a cotton swab and transported by a specialised messenger company within 12 hours to an external and independent laboratory (Balagué Center, Barcelona, Spain). Results were analysed and the growth rates of the bacterial flora were determined for each group. Samples of the bacterial flora were taken at baseline and at 3 days. In the final visit, a periapical radiograph of the implant was taken.

Statistical analysis

The sample size of the present randomised clinical trial was calculated to obtain a superiority of 15% in the number of post-operative infections in the antibiotic treatment. A one-sided type I error of 0.05 and type II error of 0.2 were assumed (assignment ratio between groups of 1.1) using the following equation:

$$n = \frac{[z_{(1-\alpha)}(2p(1-p))^{1/2} + z_{(1-\beta)}(p1(1-p1)+(p2(1-p2))^{1/2}]^2}{d^2}$$

p1: value of the proportion of post-operative infections in the antibiotic group (0.10); p2: value of the proportion in the placebo group (0.25); p: mean of p1 and p2 proportions.

A sample size of 240 patients was estimated (120 patients for each group) from which 105 patients were finally recruited from 8 of the 12 clinical centres involved in the study. Table 1 summarises the number of patients recruited at each centre.

The analysis was conduced by intention to treat. In all cases, the significance level used in statistical tests was 5% (alpha = 0.05, two-sided). Analysis of the results began with a complete descriptive analysis of the patient's demographic and clinical variables: for quantitative variables the mean value, standard deviation (SD) and range were determined, whereas for qualitative variables a frequency analysis was made. For the analysis of the primary outcome (presence of post-operative infection) the chi-square test was used.

In order to analyse the infection-free time and implant survival at the end of follow-up period, a survival analysis using the Kaplan and Meier method was used, comparing the different treatment groups using the log rank test (Cox-Mantel test). A logistic regression method was applied to determine confounding factors and the influence of different variables including the centre, treatment (antibiotic or placebo), duration of the intervention, age and smoking habits. The explicative factors were the same for the logistic regression and for the Cox regression analysis.

The analysis of variables was carried out using a descriptive analysis of the adverse events recorded in each treatment group, and then with a comparative analysis of the occurrence of opportunistic infections in each treatment group using the chi-square test.

Results

Eight out of the 12 dental clinics in Spain that agreed to participate in the RCT recruited patients and only 2 clinics recruited the agreed number of patients. A total of 105 patients were included in the study (35 men and 70 women), aged between 18 and 73 years (mean 48, SD 12 years). Fifty-two out of 105 patients received 2 g of amoxicillin orally before surgery (treatment group) while 53 patients were included in the placebo group (Fig 1). Patients were recruited and treated from January 2006 to September 2007. The follow-up period focused on the time between implant placement and 3 months after implant placement. One patient from the placebo group did not attend the last follow-up visit at 3 months for personal reasons, but until that time the implant was functional and the data was collected. In subsequent check-ups, the implant was stable and successful.

The blind conditions for 10 patients (6 in the placebo group and 4 in antibiotic group) were opened during the study, but their data was analysed. All patients received the initial treatment (antibiotic or placebo) but they received additional treatments (additional antibiotics or a new implant) due to the appearance of infection or implant failure. In fact, 2 out of the 6 patients of the placebo group had a post-operative infection and 2 of them had implant failures. In the case of the antibiotic group, 2 patients had post-operative infections and 2 had implant failures.

The number of patients recruited at each centre is summarised in Table 1. The main baseline

Centres	Placebo	Amoxicillin	Total	%
Vitoria	2	2	4	3.8
Coruña	5	4	9	8.6
Bergara	10	10	20	19.0
Irún	7	7	14	13.3
Elche	7	10	17	16.2
Albacete	10	8	18	17.1
Logroño I	2	1	3	2.9
Logroño II	10	10	20	19.0
Total	53	52	105	100.0

Table 1 Number of patients recruited at each clinical centre.

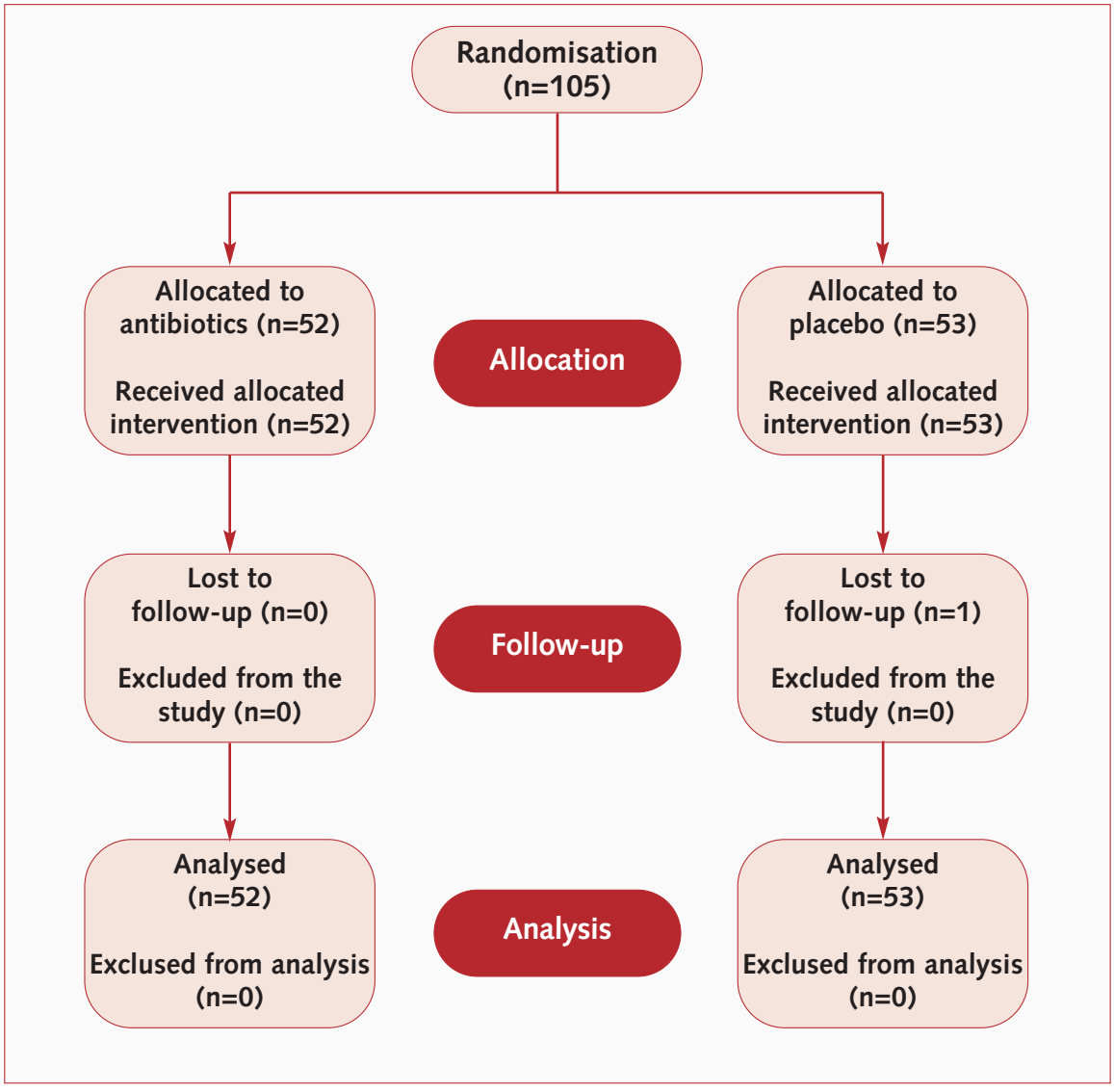

Fig 1 Scheme of the randomised clinical trial.

Table 2 Characteristics of patients and interventions between the treatment groups with amoxicillin and the placebo group.

		Amoxicillin n = 52	Placebo n = 53
Sex	Females	37 (71%)	33 (62%)
	Males	15 (29%)	20 (38%)
Mean Age		49 (±12)	47 (±12)
Smokers		10 (19%)	8 (15%)
Non-smokers		42 (81%)	45 (85%)
General health	Bad	1 (2%)	0
	Good	40 (77%)	38 (72%)
	Excellent	11 (21%)	15 (28%)
Duration of the intervention in minutes (mean value ± SD)		41.03 (±29)	41.71 (±27)
Treated jaw	Maxilla	26 (51%)	21 (40%)
	Mandible	25 (49%)	32 (60%)
Bone type	Type II	13 (25%)	10 (19%)
	Type III	38 (75%)	43 (81%)
Zone	Anterior	11 (22%)	12 (23%)
	Posterior	39 (78%)	40 (77%)
Loading type	Immediate	1 (2%)	1 (2%)

characteristics of patients and interventions are presented in Table 2. There were no baseline imbalances between the two groups. Once the follow-up period was completed, and following the criteria of infection for the present study, a total of 6 post-operative infections were observed in patients from the treatment group, whereas 6 post-operative infections were recorded in the placebo group. The full description of the post-operative infection cases observed in both groups is summarised in Table 3.

The logistic regression analysis revealed that the type of treatment applied did not significantly affect the probability of occurrence of infections either in an independent way (OR 0.97, CI 95% 0.29–3.2) or assuming the effect-modifying variables (OR 0.25, CI 95% 0.013–4.69). Similarly, the infection-free time was similar in both patient groups at the end of the follow-up period of the study: 83.45 days (CI 95% 77.12–89.8 days) in the placebo group and 83.70 days (CI 95% 76.7–90.7 days) in the group treated with amoxicillin.

The probability of not having a post-operative infection at the end of follow-up period was 88.8% in the placebo group and 87.8% in patients treated with amoxicillin (Fig 2). No statistical differences were found between both patient groups (log rank test; $P = 0.960$)

The multivariate Cox regression analysis of the different variables revealed that none of the variables were associated with an increased risk for post-operative infection (Table 4).

A total of 4 dental implants were lost during the study. Two implants were lost in the placebo group whereas 2 implants failed in the antibiotic group. Therefore, no statistically significant differences were found between both patient groups. Finally, the analysis of the saprophytic flora revealed no clinical or statistically significant differences between both groups (Table 5). The use of amoxicillin did not alter or modify the nature of the saprophytic flora (chi-square test $P = 0.362$).

Table 3 Description of the post-operative infection cases.

	Centre location	Patient age	Gender	Smoker	Surgery phase	Bone graft	Immediate loading	Intervention duration (min)
Placebo	Bergara	29	Male	No	One	No	No	120
	Elche	39	Female	No	Two	No	No	n.r.
	Logroño I	39	Female	No	One	Yes	No	60
	Bergara	57	Female	No	One	No	No	60
	Bergara	30	Female	No	One	No	No	45
	Logroño II	47	Female	Yes	One	No	No	35
Amoxicillin	Bergara	51	Male	No	One	No	No	75
	Irún	52	Female	No	One	No	No	45
	Irún	48	Female	No	Two	No	No	n.r.
	Logroño I	37	Female	No	One	Yes	No	30
	Bergara	46	Female	No	One	No	No	60
	Bergara	54	Male	No	Two	No	No	60

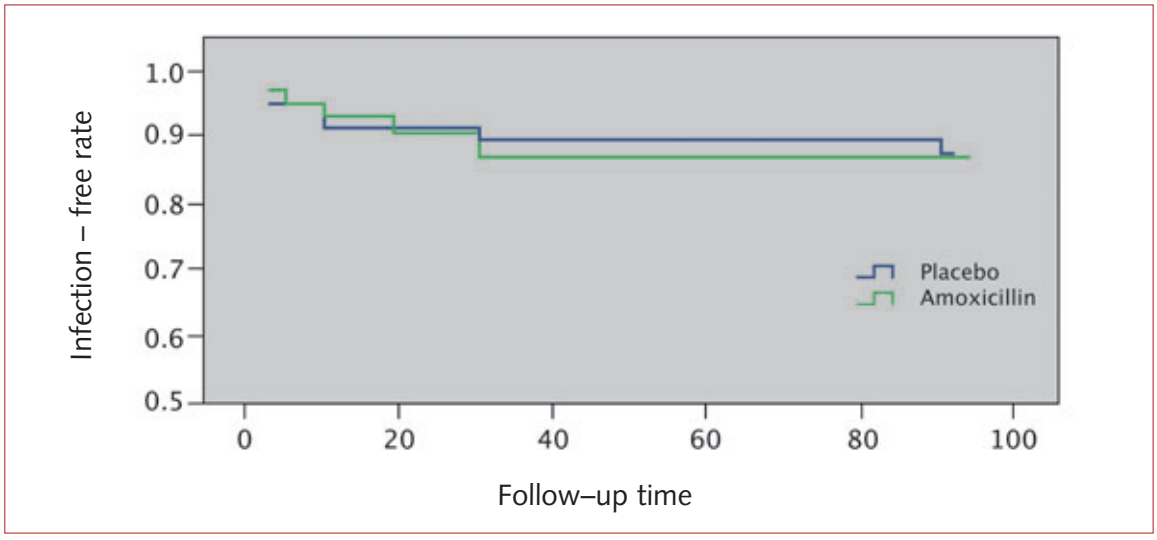

Fig 2 Infection free rate through the follow-up period.

Table 4 The multivariate Cox regression analysis of the different variables and the risk for post-operative infection.

			CI (95%)	
	Significance	Hazard Ratio	Lower	Upper
Treatment	0.092	0.176	0.023	1.325
Centre	0.958	0.000		
Intervention duration (minutes)	0.246	1.053	0.965	1.149
Age	0.316	0.945	0.846	1.055
Smoking habits	0.921	0.380	0.000	7.452
Centre x intervention duration	0.877	0.000		

Table 5 Analysis of the saprophytic flora from all patients included in the study.

	Treatment		
	Placebo	**Amoxicillin**	**Total**
Habitual mixed flora	46	39	85
Candida spp	1	2	3
Enterobacter spp	1	2	3
Enterococcus spp	0	1	1
Pseudomona spp	2	6	8
Total	53	52	105

■ Discussion

The present multicentre, placebo-controlled, double-blinded randomised clinical trial was not able to disclose any statistically significant differences when comparing patients who received 2 g of preoperative amoxicillin versus 2 g of placebo 1 hour prior to placing single dental implants. No statistically significant differences in the probability of having postoperative infection, the characteristics of the saprophytic flora of patients and the appearance of adverse effects were detected. In addition, the same number of early implant failures was recorded in both groups.

Another important finding from the present study is that none of the variables under study, including the type of treatment, the clinical centre, the intervention duration, age, smoking habits and presence of opportunistic microorganisms were statistically significantly associated with a higher risk for postoperative infection.

Interestingly, analysis of the saprophytic flora revealed no clinical or statistically significant differences between both groups under study. The use of a single dose of amoxicillin did not alter or modify the characteristics of the saprophytic flora or provoke remarkable side-effects. It is recognised that a combination of amoxicillin and clavulanic acid has a broader pharmacological spectrum, but it is also associated with an increased risk of adverse effects[13]. Therefore, in those situations requiring the use of prophylactic antibiotics, the choice of amoxicillin alone might be enough to have a suitable spectrum of action while reducing the risk of side effects.

The increase in resistance of many important pathogens to most available antibiotics has now been recognised as a universal health hazard and potentially life-threatening problem. A large number of studies strongly suggest that this increase is correlated to the use of antibiotics, whether in human or veterinary medicine. Rational use of antibiotics seeks to preserve antibiotic effectiveness against severe infections, reduce the emergence of bacterial resistance and minimise possible serious adverse reactions derived from antibiotic use. Recent data suggests that there is a general trend of providing inappropriate antibiotic prescriptions in dental practice, usually in excess, in both therapeutic and prophylactic use[5].

The high consumption of antibiotics and the rapid introduction of new antibiotic molecules to the therapeutic arsenal have led to high rates of bacterial resistance in the study's geographic area, one of the highest rates of the European Union[14]. In addition, the inappropriate use of antibiotics is not harmless and can show a negative impact both in the short and long term. Complications most commonly associated with the use of antibiotics range from diarrhoea to life-threatening allergic reactions.

The use of prophylactic antibiotics in dentistry has always been a matter of debate. Since the 90s, several prospective studies have attempted to answer this question[15-18]. Unfortunately, most of these studies were highly biased in their methodology, making their conclusions questionable.

A pilot-placebo RCT compared a preoperative single dose of 2 g phenethicillin with a placebo in 20 patients undergoing an intraoral buccal onlay graft covered with resorbable barriers to allow implant

installation. Results showed that there was a statistically significant increased risk of having a complication of infection after bone augmentation using resorbable barriers without antibiotic prophylaxis[19].

A recent double-blinded RCT concluded that no significant difference was found between prophylactic single doses of phenethicillin and clindamycin with regard to post-operative infection in patients undergoing local bone augmentation procedures[20]. Moreover, the recent trial reported by Esposito et al evaluated the efficacy of prophylactic antibiotics for dental implant placement[7]. In parallel to the present results, authors did not observe statistically significant differences for implant losses, complications and side effects. They also found an increased risk of early implant failure in patients from the placebo group compared to those who received prophylactic antibiotics (8 versus 2 patients, $P = 0.104$). The authors suggested that further investigations were needed. In another RCT reported by Abu Ta'a, the authors showed more implant failures in the absence of antibiotics[8]. In these studies, any patient requiring dental implants was evaluated, including fully edentulous patients, whereas in the present RCT only patients needing single implant placement were recruited. By combining these two studies in a meta-analysis, there were statistically significantly more implant failures in the group without antibiotics.

Results from the present study are different than those published in the previous RCTs. One explanation for this could be that in the present RCT only patients with bone types II and III were selected. It may be possible that the inclusion of bone types I and IV, which in general implicate more surgical difficulties, could have altered the final results. In addition, it must be emphasised that the present study has not achieved a sufficient sample size to detect a statistically significant difference. Only half of the planned number of patients were recruited, with only two centres recruiting the required number of patients.

In summary, the present trial aimed to shed light on the use of prophylactic antibiotics in the placement of single implants. The study was conducted using placebo tablets identical to the amoxicillin tablets and patients and investigators were blinded for the entire duration of the trial. The inclusion criteria were rather strict since bone types I and IV were excluded and only patients treated with single implants were considered, thus limiting the extrapolation of the present results to other settings.

Conclusions

There were no statistically significant differences for post-operative infection, adverse events, implant failures and the characteristics of saprophytic flora when using a single oral dose of 2 g of amoxicillin versus 2 g of placebo 1 hour prior to placement of single implants in bone types II and III. The use of amoxicillin did not alter or modify the characteristics of the saprophytic flora or provoke remarkable side effects. The same number of early implant failures was recorded in both groups of the study. None of the variables studied were statistically significantly associated with a higher risk for post-operative infection. No major side effect related to the use of antibiotics occurred. According to these limited data, antibiotic prophylaxis may not be needed when placing single implants in bone types II and III using implants covered with PRGF.

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