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RESEARCH

Effects of clindamycin and amoxycillin as prophylaxis against early implant failure: double-blinded randomized clinical trial

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Abstract

Objective The objective of this randomized controlled clinical trial (RCT) was to compare the frequency of early implant failure, postoperative infection, and pain/inflammation and the degree of implant stability between healthy non-penicillin-allergic individuals receiving a single prophylactic dose of 600 mg clindamycin *versus* 2 g amoxicillin at 1 h before implant surgery.

Materials and methods A single-center double-blinded RCT study with parallel groups was undertaken. Eighty-two patients fulfilled study inclusion criteria and were randomly assigned to the amoxicillin ($n=41$) or clindamycin ($n=41$) group. The primary outcome variable was early implant failure. The presence of infection was evaluated immediately after surgery and on days 7, 14, 30, and 90, and postoperative pain/inflammation was assessed daily on days 1 to 7 post-surgery. Resonance frequency analysis was used to measure primary and secondary implant stability.

Results One early implant failure was observed (1/81), in a patient from the amoxicillin group. No statistically significant between-group differences were observed in early implant failure rate, postoperative infection rate up to 90 days, pain/inflammation scores during the first week post-surgery, or primary or secondary stability values.

Conclusions A single dose of 600 mg clindamycin before implant surgery does not increase the risk of early implant failure or infection.

Clinical relevance These findings suggest that a single dose of 600 mg clindamycin at 1 h before implant surgery is a safe antibiotic prophylactic approach; however, when a more prolonged antibiotic therapy is required, it appears advisable to prescribe an alternative antibiotic to avoid adverse effects.

Keywords Clindamycin · Amoxicillin · Implant failure · Prophylaxis · RCT

Introduction

Dental implants are frequently placed to rehabilitate partially or totally edentulous dental arches and have a reported 10-year survival rate of between 95.2% and 97.5% [1]. Implant failure can be classified as early or late [2]. Early failure is defined by implant mobility or by the need for its removal due to inadequate bone healing during the first few months after placement, preventing prosthetic loading [3, 4]. Various factors may be implicated in the failure to achieve osseointegration, including a lack of primary stability, bacterial contamination during implant placement, tobacco smoking, non-controlled periodontitis, poor bone quality, or implants that are too short [3, 5–7]. Late failure is defined by loss of the implant after prosthesis loading and is related not only to biological factors, such as bacterial infection and

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the possible development of "peri-implantitis", but also to mechanical factors, including poor prosthesis design, screw fracture, or implant fracture [8].

The oral cavity harbors more than 600 bacterial strains that can contribute to osseointegration contamination and loss during implant placement [9]. Multiple preoperative and postoperative antibiotic therapies have been proposed in implant surgery for systemically healthy people [10, 11] to prevent early failure due to bacterial contamination. However, this antibiotic prophylaxis is only currently recommended in individuals at risk of endocarditis, immunosuppressed individuals, those undergoing surgery that is extensive and prolonged or involves an infected area, and in those implanted with large-size biomaterials [10, 12].

Antibiotic prophylaxis for implant placement in healthy individuals is well documented but remains controversial due to the possible risk of hypersensitivity, allergies, serum alterations, direct organ damage, and superinfections [13, 14]. Its potential role in the spread of antibiotic-resistant bacteria has also been highlighted [15]. Furthermore, some researchers found no statistically significant difference in postoperative infection or complication rates between healthy individuals receiving and not receiving antibiotic prophylaxis [16]. However, recent reviews and meta-analyses have concluded that the likelihood of early implant failure is significantly reduced by a single antibiotic dose, commonly 2 g amoxicillin administered at 1 h before implant surgery [17–22]. Amoxicillin is the most widely prescribed antibiotic for this purpose, but dose regimens vary among different countries, and no consensus has been achieved on the optimal approach [23, 24].

In individuals with an allergy to penicillin, the most frequently prescribed antibiotic is clindamycin, administering a dose of 600 mg at 1 h before implant placement [17, 18, 25, 26]. Between 8 and 10% of the general population are considered allergic to penicillin [27] and appear to be more prone to implant failure and postoperative infection [28]. Studies [29–32] in allergic patients found that implant failure predominantly occurs during the osseointegration period. The authors called the prophylactic effect of clindamycin into question, suggesting that it may be responsible for the higher rates of early implant failure and postoperative infection in penicillin-allergic individuals. However, research to date has generally been retrospective, and randomized clinical trials (RCTs) are needed to elucidate this issue.

The objective of this RCT was to compare the frequency of early implant failure, postoperative infection, and pain/inflammation and the stability of implants between healthy non-penicillin-allergic individuals receiving a single prophylactic dose of 600 mg clindamycin *versus* 2 g amoxicillin at 1 h before implant surgery.

Materials and methods

Study design and patient selection

A single-center double-blinded RCT with parallel groups was undertaken in patients treated at the Clinic of the Masters in Oral Surgery and Implantology of the University of Granada. Study inclusion criteria were age ≥ 18 years, absence/control of periodontal disease, need for single implant placement in molar or premolar, and the presence of sufficient bone and soft tissue, with no need for augmentation. Exclusion criteria were the requirement for postoperative antibiotic prophylaxis (e.g., in immunosuppressed patients); receipt of head and neck radiotherapy in past two years; smoking habit; history of *Clostridium difficile* infection or ulcerous colitis; the presence of diabetes (controlled or non-controlled); allergy to penicillin, clindamycin, and/or clavulanic acid; receipt of antiresorptive medication; pregnancy or breast-feeding; antibiotic treatment for other reasons; post-extraction implantation or immediate implant loading; need for simultaneous bone regeneration or implantation at sites previously treated with bone regeneration.

All participants signed informed consent to participate in the study, which complied with the ethical principles of the Helsinki Declaration. The trial was approved by the Human Research Ethics Committee of the University of Granada (1016 CEIH/2019) and registered in the Clinical Trial Registry of Australia and New Zealand (ANZCTR; No. ACTRN12624000324516), and the recommendations of the CONSORT 2010 statement for RCT reporting were followed [33, 34].

The sample size was estimated in accordance with Wittes guidelines [35]. Values published by Edibam et al. (2023) were used to calculate the sample size for a fixed power of 80% and a statistical significance of 5%, considering failure rates of 3% overall, 9% for clindamycin, and 3% for amoxicillin. A sample size of 74 patients was estimated and increased by 10% to 82 patients to cover possible losses, i.e., 41 per group. Patients were consecutively enrolled up to the total of 82 by balanced randomization every 8 patients (4 patients per group), using a computer-generated randomization sequence. Each participant was assigned (1:1 ratio) a random code (A or B), with code A representing the amoxicillin group for the receipt of 1 oral capsule of 2 g amoxicillin (Kern Pharma, Spain) and code B the clindamycin group for the receipt of 1 oral capsule of 600 mg clindamycin (Normon, Spain), always at 1 h before implant surgery. Assignments were stored in numbered sealed opaque blisters and opened 1 h before surgery by a clinician who administered the medication but was not involved in the perioperative evaluation of patients. All capsules were identical in size, color, and shape to ensure blinding. All data were gathered

by the main researcher (D.P.G.), a specialist in oral and implant surgery with experience in randomized clinical trials, who did not perform the surgery and was blinded to the group assignment of patients, as were all patients and surgeons involved in the study. Finally, the statistics consultant was also unaware of the group to which patients belonged until completion of the study.

Surgical protocol

All surgical procedures were conducted by two experienced surgeons (FJ.M.M., MV.O.G.) with similar levels of training and experience. Immediately before the surgery, patients rinsed their mouths for 60 s with 0.12% chlorhexidine (Perio-Aid; Dentaid, Barcelona, Spain) and received local anesthesia using 4% articaine with 1: 100,000 epinephrine (Ultracain; Normon, Madrid, Spain). The incision was performed with or without releasing incisions according to the local anatomy, bone availability, adjacent teeth, and patient esthetics, accompanied by mucoperiosteal flap elevation. The socket was drilled as a function of implant diameter and bone type, following the manufacturer's instructions. The Zimmer Biomet Tapered Screw-Vent® (TSV) system (Warsaw, IN) was used in all patients. After the implantation, resonance frequency analysis (RFA) was performed with the Osstell IDx® system (Osstell, Gothenburg, Sweeden) to assess the primary implant stability, expressed as implant stability quotient (ISQ). Finally, the area was closed without tension using 5/0 non-resorbable polyamide sutures (Seralon; Osteógenos, Madrid, Spain). The patient was then given instructions on postoperative care, including a mouthwash with 0.12% chlorhexidine twice daily for the first week, and on pain management, prescribing 400 mg ibuprofen or 1 g paracetamol every 8 h when required. Sutures were removed at one week post-surgery. Patients with postoperative infection were treated with amoxicillin-clavulanic acid (875/125 mg) every 8 h for one week.

Follow-up examinations were conducted immediately after the surgery and at 7, 14, 30, and 90 days. The healing abutment was placed in a second surgical phase at 90 days, and the secondary implant stability (ISQ value) was measured with the Osstell IDx® system (Osstell, Gothenburg, Sweden).

Study variables

The primary outcome variable was early implant failure, defined by removal of the implant before prosthetic loading. Data were also gathered on the presence of postoperative infection at days 7, 14, 30, and 90 post-surgery, identified by persistent pain after the first 48–72 h, inflammation at day 7 post-surgery, fever (> 38 °C), heat, suppuration, erythema, and/or the presence of peri-implant radiolucency. Postoperative pain and inflammation were evaluated daily on days 1 to 7 post-surgery using a VAS (0 = no pain/swelling to 10 = maximum imaginable pain/swelling), also recording the amount of anti-inflammatory/analgesic rescue medication taken each day. In addition, ISQ values for primary and secondary implant stability were collected, and any adverse events (e.g., nausea, vomiting, diarrhea, exanthema, dyspepsia, or acidity) were recorded.

Information was collected on the patient's age, sex, general health (American Society of anesthesiologist [ASA] I or ASA II), systemic medication (yes/no), oral hygiene quality by the O'Leary index [36] (excellent/good/poor), history of periodontitis (yes/no), implant site (posterior maxilla/posterior mandible), and implant bed bone quality (type I, II, III, or IV in the Lekholm and Zarb classification [37]). Further data were obtained on the length (8–10 mm/>10 mm) and diameter (3.1 mm/3.7–4.1 mm/4.7 mm) of the implant, the type of incision (none, linear without releasing incision, or linear with releasing incision), the performance of bone augmentation/condensation (yes/no) or atraumatic sinus elevation (yes/no), and the duration of surgery (in min).

Statistical analysis

SPSS v 29.0 (IBM SPSS, Armonk, NY) was used for the statistical analysis. Arithmetic means with standard deviations were calculated for quantitative variables, checking the normality of variable distribution with the Shapiro-Wilk test. Qualitative variables were expressed as relative frequency (%) and relative risk and in contingency tables. Comparisons were performed using the Mann-Whitney U test or Student's t-test, as appropriate. Associations between qualitative variables were examined with the Fisher test (for 2 × 2 tables) or chi-square test. $\alpha = 0.05$ was considered significant.

Results

Eighty-two patients fulfilled the study inclusion criteria and were randomly assigned to the amoxicillin-treated group ($n = 41$) or clindamycin-treated group ($n = 41$). The final sample comprised 81 patients, after one patient in the clindamycin group moved away from the area and was lost to the follow-up. ISQ data for secondary stability are missing for five patients in the clindamycin group and one in the amoxicillin group, who completed the follow-up but received rehabilitation treatment at a different clinic. Figure 1 depicts the flow of patients through the study.

As shown in Table 1, the mean age of participants was 50.63 ± 11.67 years, 39 (48.1%) patients were males and 42

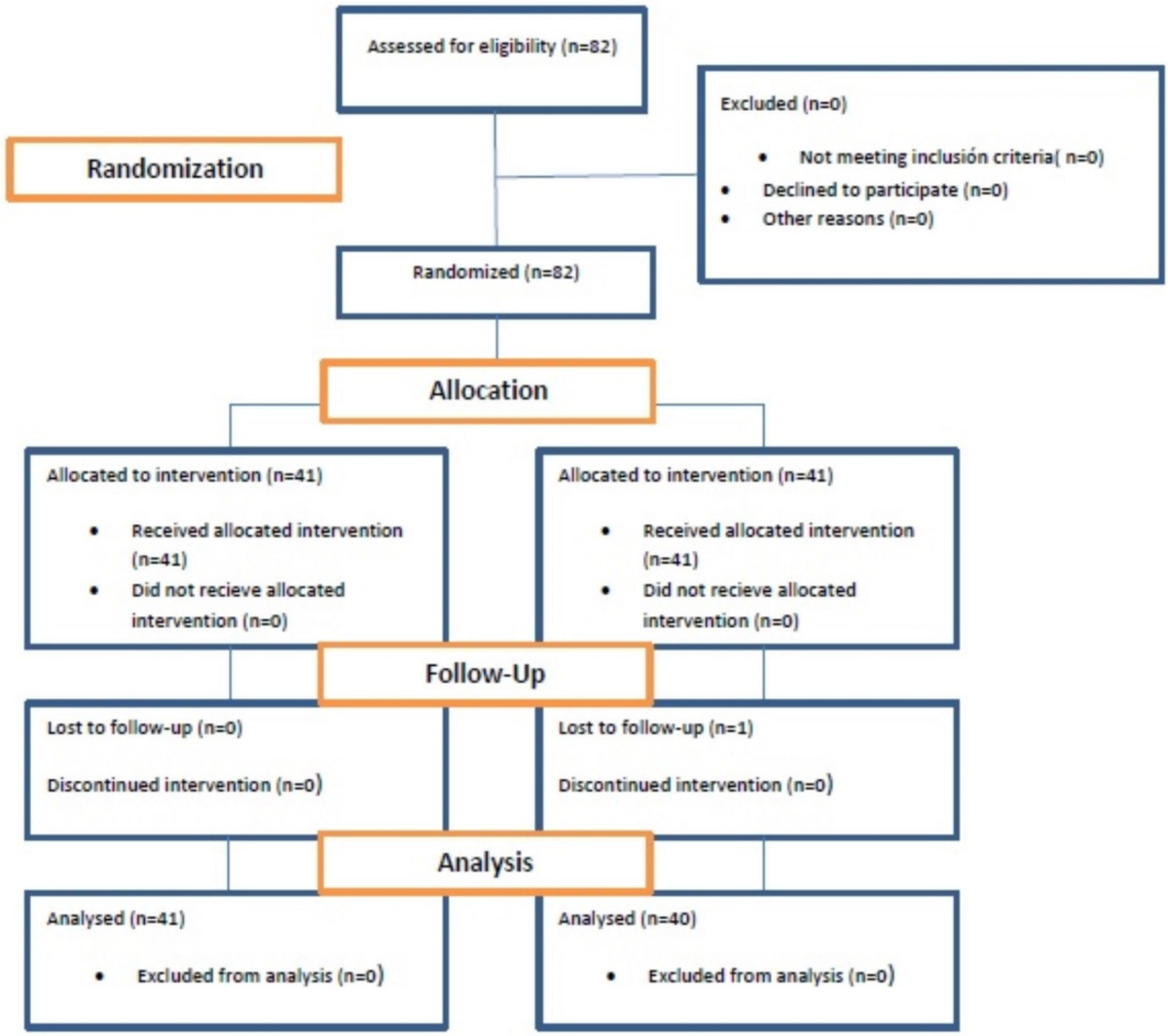

Fig. 1 Flow chart of the enrolment process

(51.9%) females; 55 patients were ASA I (67.9%) and 26 (32.1%) ASA II; 25 (30.9%) patients were receiving systemic medication and 56 (69.1%) were not; 12 (14.8%) patients had (controlled) periodontal disease and 69 (85.2%) did not; 38 (46.9%) implants were placed in posterior maxilla and 43 (53.1%) in posterior mandible; 9 (11.1%) implants were placed in type I, 28 (34.6%) in type II, 36 (44.4%) in type III, and 8 (9.9%) in type IV bone. The mean surgery duration was 32.42 ± 17.68 min overall, 32.98 ± 16.51 min for the amoxicillin group, and 31.85 ± 18.99 min for the clindamycin group. Results for remaining surgical and implant variables are displayed in Table 2. All study variables were homogeneously distributed between treatment groups, with no statistically significant differences ($p > 0.05$).

There was only one early implant failure (1/81), in a patient from the amoxicillin group; however, there was no statistically significant difference in early implant failure rate between treatment groups. Postoperative infection was observed in one patient from each treatment group at day 7 post-surgery, in one patient from the clindamycin group at day 14, and in one from the amoxicillin group at day 30. No implant failed in patients with postoperative infection. There was no statistically significant between-group difference in postoperative infection at days 7, 14, 30, or 90 (Table 3).

Although postoperative infection was more frequently observed in females *versus* males, in ASA II *versus* ASA I patients, in systemically-medicated *versus*

Table 1 Patient characteristics

Variable		Amoxicillin group ($n=41$)	Clindamycin group ($n=40$)	*P* value	Global ($n=81$)
Age		50.37 ± 11.07	50.90 ± 12.4	0.814*	50.63 ± 11.67
Sex	Male	22 (53.7%)	17 (42.5%)	0.377	39 (48.1%)
	Female	19 (46.3%)	23 (57.5%)		42 (51.9%)
General health	ASA I	30 (73.2%)	25 (62.5%)	0.347	55 (67.9%)
	ASA II	11 (26.8%)	15 (37.5%)		26 (32.1%)
Systemic medication	Yes	11 (26.8%)	14 (35%)	0.477	25 (30.9%)
	No	30 (73.2%)	26 (65%)		56 (69.1%)
Oral hygiene quality	Excellent	8 (19.5%)	7 (17.5%)	0.922	15 (18.5%)
	Good	28 (68.3%)	27 (67.5%)		55 (67.9%)
	Poor	5 (12.2%)	6 (15%)		11 (13.6%)
Periodontitis	Yes	8 (19.5%)	4 (10%)	0.349	12 (14.8%)
	No	33 (80.5%)	36 (90%)		69 (85.2%)
Implant localization	Posterior maxilla	18 (43.9%)	20 (50%)	0.659	38 (46.9%)
	Posterior mandible	23 (56.1%)	20 (50%)		43 (53.1%)
Bone type	Type I	7 (17.1%)	2 (5%)	0.190	9 (11.1%)
	Type II	14 (34.1%)	14 (35%)		28 (34.6%)
	Type III	18 (43.9%)	18 (45%)		36 (44.4%)
	Type VI	2 (4.9%)	6 (15%)		8 (9.9%)

*P-value obtained with the Mann-Whitney U test. Other p-values obtained with Fisher's exact test

Table 2 Surgical variables by treatment group

Variable		Amoxicillin group ($n=41$)	Clindamycin group ($n=40$)	*p*-value	Global ($n=81$)
Implant length	8–10 mm	39 (95.1%)	38 (95%)	1.000	77 (95.1%)
	> 10 mm	2 (4.9%)	2 (5%)		4 (4.9%)
Implant diameter	3.1 mm	1 (2.4%)	0	0.592	1 (1.2%)
	3.7–4.1 mm	29 (70.7%)	28 (70%)		57 (70.4%)
	4.7 mm	11 (26.8%)	12 (30%)		23 (28.4%)
Type of incision	No incision	4 (9.8%)	5 (12.5%)	0.513	9 (11.1%)
	Linear	36 (87.8%)	32 (80%)		68 (84%)
	Linear with releasing incisions	1 (2.4%)	3 (7.5%)		4 (4.9%)
Expansion/condensation	Yes	2 (4.9%)	5 (12.5%)	0.264	7 (8.6%)
	No	39 (95.1%)	35 (87.5%)		74 (91.4%)
Transcrestal sinus elevation	Yes	5 (12.2%)	5 (12.5%)	1.000	10 (12.3%)
	No	36 (87.8%)	35 (87.5%)		71 (87.7%)
Surgery duration		32.98 ± 16.511	31.85 ± 18.99	0.259*	32.42 ± 17.68

*P-value obtained with the Mann-Whitney U test. Other p-values obtained with Fisher's exact test

non-systemically-medicated patients, and in implants placed in mandible *versus* maxilla, the only statistically significant difference was between patients with *versus* without periodontal disease, observing a 22-fold higher risk of postoperative infection in the former (Table 4).

There were no statistically significant between-group differences in inflammation/pain scores or in rescue medication consumption during the first week post-surgery. Some rescue medication was consumed by all patients (Table 5).

At day 90, the mean ISQ value had increased by 4.64 ± 6.60 in the amoxicillin group and 4.94 ± 6.83 in the clindamycin group in comparison to the baseline value at surgery. A higher baseline ISQ was significantly associated ($p<0.001$) with the value at day 90 in both groups, and there was no statistically significant between-group difference ($p=0.854$). The 90-day increase in ISQ did not significantly differ between treatment groups as a function of bone type or implant site (Table 6). Globally, the 90-day increase in ISQ did not significantly differ ($p=0.428$) between implants in maxilla (4.74 ± 5.53) versus mandible (4.82 ± 7.62). However, significantly higher ISQ values were recorded for both primary ($p=0.042$) and secondary ($p=0.002$) stability in implants in mandible *versus* maxilla. Finally, the 90-day ISQ increase was significantly greater ($p<0.05$) for implants in type IV *versus* types I, II, or III bone.

Table 3 Secondary outcome variables

Follow up		Heat	Suppuration	Inflammation	Pain	Fever > 38 °C	Erythema	Presence of infection
	Amoxicillin	1/41	0/41	1/41	1/41	0/41	1/41	1/41
Day 7	Clindamycin	0/40	0/40	1/40	1/40	0/40	0/40	1/40
	p- value	1	-	1	1	-	1	1
	Amoxicillin	0/41	0/41	0/41	0/41	0/41	0/41	0/41
Day 14	Clindamycin	0/40	0/40	1/40	1/40	0/40	0/40	1/40
	p-value	-	-	0.494	0.494	-	-	0.494
	Amoxicillin	1/41	0/41	1/41	1/41	0/41	1/41	1/41
Day 30	Clindamycin	0/40	0/40	0/40	0/40	0/40	0/40	0/40
	p-value	1	-	1	1	-	1	1
	Amoxicillin	0/41	0/41	0/41	0/41	0/41	0/41	0/41
Day 90	Clindamycin	0/40	0/40	0/40	0/40	0/40	0/40	0/40
	p-value	-	-	-	-	-	-	-

P-values obtained with Fisher's exact test

Table 4 Main outcome variables

Variable		Early failure			Postoperative infection		
		Proportion	OR (95% CI)	P value	Proportion	OR (95% CI)	P value
Treatment group	Clindamycin	0/40	NA	0.961	2/40	1.026(0.137–7.662)	1.000
	Amoxicillin	1/41			2/41		
Sex	Male	1/39	NA	> 0.05	0/39	NA	0.117
	Female	0/42			4/42		
General health	ASA I	1/55	NA	> 0.05	1/55	0.142(0.014–1.438)	0.095
	ASA II	0/26			3/26		
Systemic medication	Yes	0/25	NA	> 0.05	3/25	7.500(0.740-76.055)	0.085
	No	1/56			1/56		
Oral hygiene quality	Excellent	0/15	NA	> 0.05	2/15	NA	> 0.05
	Good	1/55			2/55		
	Poor	0/11			0/11		
Periodontal disease	Yes	0/12	NA	> 0.05	3/12	22.667(2.124–241.880)	0.009
	No	1/69			1/69		
Implant localization	Posterior maxilla	1/38	NA	> 0.05	0/38	NA	0.119
	Posterior mandible	0/43			4/43		
Bone type	I	0/9	NA	> 0.05	0/9	NA	> 0.05
	II	1/28			0/28		
	III	0/36			3/36		
	IV	0/8			1/8		
Implant length	8–10 mm	1/77	NA	> 0.05	4/77	NA	> 0.05
	> 10 mm	0/4			0/4		
Implant diameter	3.1 mm	0/1	NA	> 0.05	0/1	NA	> 0.05
	3.7–4.1 mm	0/57			3/57		
	4.7 mm	1/23			1/23		
Incision type	No incision	0/9	NA	> 0.05	0/4	NA	> 0.05
	Linear	1/68			4/68		
	Linear with releasing incisions	0/4			0/4		
Expansion/condensation	Yes	0/7	NA	> 0.05	0/7	NA	> 0.05
	No	1/74			4/74		
Transcrestal sinus elevation	Yes	1/10	NA	> 0.05	0/10	NA	> 0.05
	No	0/71			4/71		

P-values obtained with Fisher's exact test

CI: confidence interval; NA: not assessable

Table 5 Secondary outcome variables during first week of follow-up

Follow up		Amoxicillin (Mean ± SD)	Clindamycin (Mean ± SD)	*P*-value
	Mean pain (0–10 scale)	3.83 ± 1.97	3.20 ± 1.96	0.218
Day 1	Mean inflammation (0–10 scale)	3.17 ± 2.11	2.58 ± 2.35	0.137
	Nº pills	2.20 ± 1.14	1.78 ± 1.19	0.203
	Mean pain (0–10 scale)	2.71 ± 2.03	2.15 ± 2.09	0.152
Day 2	Mean inflammation (0–10 scale)	2.41 ± 1.91	1.95 ± 2.42	0.110
	Nº pills	1.61 ± 1.48	1.23 ± 1.21	0.277
	Mean pain (0–10 scale)	1.27 ± 1.61	0.90 ± 1.48	0.242
Day 3	Mean inflammation (0–10 scale)	1.10 ± 1.51	0.98 ± 1.90	0.315
	Nº pills	0.98 ± 1.25	0.73 ± 1.09	0.323
	Mean pain (0–10 scale)	0.76 ± 1.48	0.45 ± 0.93	0.550
Day 4	Mean inflammation (0–10 scale)	0.83 ± 1.48	0.65 ± 1.72	0.311
	Nº pills	0.63 ± 1.20	0.40 ± 0.93	0.192
	Mean pain (0–10 scale)	0.37 ± 1.22	0.20 ± 0.61	0.769
Day 5	Mean inflammation (0–10 scale)	0.44 ± 1.34	0.33 ± 1.05	0.577
	Nº pills	0.32 ± 0.99	0.25 ± 0.74	0.987
	Mean pain (0–10 scale)	0.15 ± 0.57	0.13 ± 0.52	0.992
Day 6	Mean inflammation (0–10 scale)	0.29 ± 0.96	0.23 ± 0.80	0.749
	Nº pills	0.07 ± 0.47	0.13 ± 0.46	0.314
	Mean pain (0–10 scale)	0.07 ± 0.35	0.10 ± 0.38	0.634
Day 7	Mean Inflammation (0–10 scale)	0.17 ± 0.59	0.18 ± 0.59	0.971
	Nº pills	0.07 ± 0.47	0.13 ± 0.46	0.314

P-values obtained with the Mann-Whitney U test

SD: standard deviation

Ony one adverse reaction (exanthema) was recorded, in a patient from the clindamycin group, and there was no statistically significant between-group difference in this variable.

Discussion

In this clinical trial, no difference in early implant failure rate was observed between non-penicillin-allergic individuals receiving single-dose prophylaxis of 2 g amoxicillin *versus* 600 mg clindamycin at 1 h before implant surgery. Results for postoperative infection, pain, and inflammation were also similar between the treatment groups, with no difference in rescue medicine consumption during the first week. In addition, no between-group difference was observed in primary or secondary stability values. Although no patient had non-controlled periodontal disease, an association was observed between (controlled) periodontal disease and the presence of postoperative infection.

Out of a total of eighty-one implants, only one failed before loading, a lower early failure rate than reported in recent RCTs [38–40]. This may be attributable to our exclusion of individuals with known risk factors, i.e., tobacco smokers [41], individuals with post-extraction implants [42, 43] or implants on regenerated bone [44], and those with non-controlled periodontal disease [3]. In addition, the fact that both groups received antibiotic prophylaxis would reduce the risk of early failure, as established by multiple systematic reviews and meta-analyses [17–20, 22]. Although antibiotic prophylaxis has long been used to prevent early implant failure [10–12], the current trend is to forego its administration before implant surgery in systemically healthy patients [25]. Nevertheless, the main objective of this clinical trial was not to test the efficacy of antibiotic prophylaxis to reduce implant failure risk but rather to compare outcomes in non-allergic patients between the presurgical administration of clindamycin and that of amoxicillin, the current antibiotic of choice. This is because the utilization of clindamycin in penicillin-allergic patients may

Table 6 Comparison between ISQ values at day 90 and baseline by bone type and implant site

			Amoxicillin (Mean ± SD)	Clindamycin (Mean ± SD)	*P*-value	Total (Mean ± SD)
Day-90 ISQ– baseline ISQ			4.64 ± 6.60	4.94 ± 6.83	0.854	4.78 ± 6.66
	Bone type	I	2.29 ± 2.81	0.50 ± 0.71	0.500	1.88 ± 2.57
		II	3.42 ± 6.39	4.08 ± 3.86	0.769	3.76 ± 5.12
		III	6.22 ± 7.38	3.00 ± 5.83	0.274	4.75 ± 6.81
		IV	6.00 ± 11.31	14.80 ± 9.20	0.571	12.28 ± 9.81
	Implant site	Posterior maxilla	5.24 ± 6.16	4.28 ± 4.99	0.883	4.74 ± 5.53
		Posterior mandible	4.18 ± 7.03	5.65 ± 8.46	0.878	4.82 ± 7.62

P-values obtained with the Mann-Whitney U test

SD: standard deviation

be related to higher early implant failure and postoperative infection rates [28, 45].

In the only comparable RCT, published by Santamaría Arrieta et al. in 2023 [40], no significant difference in early implant failure or the presence of postoperative infection was found between individuals receiving 600 mg clindamycin *versus* placebo at 1 h before surgery. In their meta-analysis, Edibam et al. [45] reported that the risk of implant failure was 3.3-fold higher in penicillin-allergic individuals receiving clindamycin than in non-allergic individuals receiving amoxicillin and that 80% of the increased failure in penicillin-allergic individuals was early [29–31]. The degree to which the early implant failure rate in penicillin-allergic patients is influenced by the effects of clindamycin has not been established. The articles in the meta-analysis [45] are all retrospective observational studies [29–32], and there is a need for RCTs to yield evidence of higher quality.

In their review, Salgado-Peralvo et al. [28] proposed possible causes of this increased early failure rate in allergic patients. They implicated the non-optimal effectiveness of clindamycin in the possible generation at day 10 post-intake of resistant strains of *Prevotella* (e.g., *P.intermedia* and *P.aeruginosa*), which have been detected in cases of peri-implantitis [46]. Chronic exposure to this antibiotic would favor the early development of clindamycin-resistant bacteria in penicillin-allergic patients [47, 48].

In comparison to amoxicillin, clindamycin has been described as less effective to treat odontogenic infections, requiring a longer regimen and more frequently failing in comparison to amoxicillin-clavulanate [48]. This might explain the higher risk of post-implant infection in penicillin-allergic individuals under longer-term treatment with clindamycin [28]. Diz Dios et al. [49] found that prophylaxis before tooth extraction with either amoxicillin or moxifloxacin significantly reduced the frequency of bacteremia but that prophylactic treatment with clindamycin (600 mg) did not. None of the participants in the present RCT were allergic to penicillin, and no difference in postoperative infection rate was observed between clindamycin and amoxicillin as prophylaxis before implant surgery. Lindeboom et al. [50] also studied non-penicillin-allergic individuals and found no significant difference in postoperative infection rate between prophylaxis with 2 g penicillin *versus* 600 mg clindamycin at 1 h before bone regeneration surgery [50]. The postoperative infection rate in the present RCT was higher than that observed in recent clinical trials (2/40 vs. 1/31 vs. for clindamycin [40] and 2/41 vs. 7/238 amoxicillin, respectively [38]), although it was similar to the rates obtained in the placebo groups in these trials (2/31 [40] and 12/235 [38]). These findings would support the non-administration of antibiotic prophylaxis to systematically healthy patients, as proposed by Khouly et al. [16]. Postoperative infection was associated with the presence of periodontal disease, even though the disease was always controlled in the present patients. In their study in a hospital setting, Cueto Urbina et al. [51] also found an association between periodontal disease and a higher rate of postoperative complications. In addition, Sakkas et al. [52] reported that the presence of periodontal disease increased the risk of complications after regenerative surgery with autologous bone. All postoperative infections in the present study were in patients with mandibular implants, whereas all three cases of postoperative infection described by Santamaría Arrieta et al. [40] involved maxillary implants.

No significant difference was found between the present treatment groups in inflammation/pain scores or rescue medication intake during the first week post-surgery, although a non-significantly higher number of pills were taken by patients in the amoxicillin group. In this regard, Escalante et al. [53] observed a higher concentration of pro-inflammatory mediators during early implant healing in patients receiving prophylactic treatment with amoxicillin rather than azithromycin, implying slower inflammation resolution and healing. Clindamycin continues to be highly frequently prescribed and is the most widely used antibiotic for prophylaxis in dental implantation surgery [54]. However, azithromycin is emerging as a possible alternative in penicillin-allergic patients to reduce the risks of *C. difficile*–induced pseudomembranous colitis [55], early implant failure, and post-operative infection [56].

In the present trial, the increased RFA-measured ISQ at day 90 did not significantly differ between the treatment groups, indicating that a similar degree of implant osseointegration is achieved with a single prophylactic dose of either 2 g amoxicillin or 600 mg clindamycin at 1 h before implant placement. However, it has been proposed that clindamycin may impair osseointegration, and this antibiotic has been implicated [29–31, 45] in implant failure in penicillin-allergic individuals. In vitro studies have described a cytotoxic effect of this antibiotic on osteoblasts [57] at high concentrations and a possible negative impact on osteoblast differentiation and proliferation [58]. However, consideration should be made of the peri-implant concentrations of clindamycin and the effects of prolonged exposure on osteointegration. Schüssl et al. [59] administered a prophylactic dose of 2 g amoxicillin or 600 mg clindamycin at least 1 h before tooth extraction and observed mean concentrations of 18.2 µg/mL amoxicillin or 9.53 µg/mL clindamycin in post-extraction sockets, with maximum concentrations of 32.5 µg/mL amoxicillin or 16.3 µg/mL clindamycin. Similar values were reported by Bouazza et al. [60], who compared between the oral and intravenous administration of 600 mg clindamycin to treat osteomyelitis and described a maximum serum concentration of 16 µg/mL after oral administration and

18 µg/mL after intravenous administration. Concentrations of at least 400–500 µg/mL are considered cytotoxic due to increased lactate dehydrogenase (LDH) levels [57, 58], and infinitely lower blood and bone concentrations are observed after a single dose of 600 mg clindamycin [59, 60]. In their in vitro study, Duewelhenke et al. [57] found no changes in cytotoxicity (LDH), proliferation (bromodeoxyuridine [BrdU]), or metabolic activity (MTT) in primary human osteoblasts treated with concentrations < 25 µg/mL for 24 h but observed a dose-dependent reduction in osteoblast activity when these concentrations were maintained for six days. Likewise, Naal et al. [58] observed that a concentration of 10 µg/mL produced no changes in cell proliferation (MTT) or cytotoxicity (LDH) at 24 h, although there was an increase in osteoblast metabolic activity (alkaline phosphatase activity); however, cell proliferation and activity were reduced after exposure for 72 h *versus* 24 h or 48 h.

The immune system plays a critical role in osseointegration, and an imbalance in the inflammatory process may trigger the encapsulation and non-osseointegration of implants [61]. T-CD4 lymphocytes have been found to interfere with the regulation of osteoclast and osteoblast activity, affecting bone development, homeostasis, and healing [61, 62]. Ahmad et al. [63] observed an altered T-cell response after implant surgery in mice under prolonged clindamycin or amoxicillin treatment with the suppression of TH1, TH2, and TREG cells, which contribute to bone metabolism healing. They described a decrease in osteoblast count and osteoclast size at the bone-implant interphase in both treatment groups, with lower bone-to-implant contact values in comparison to placebo-treated mice.

Besides the possible effects of clindamycin, penicillin allergy may itself predispose patients to early implant failure. In this way, the systematic review by Ferrer et al. [64] reported that polymorphisms G-1607GG of MMP 1 gene, C-799T of MMP 8 gene, and − 77 A > G of MMP 13 gene were associated with extracellular matrix inflammation and degradation, which would favor early implant failure. A possible association should also be considered between penicillin allergy and titanium allergy, although this is rarely encountered, given reports of a genetic relationship between allergy to penicillin and allergy to nickel or cobalt [65, 66]. Future studies are warranted to investigate the relationship between these polymorphisms and penicillin allergy.

Almost all retrospective studies reporting a higher implant failure rate in allergic *versus* non-allergic individuals administered prophylactic treatment with 600 mg clindamycin and then maintained this regimen for 7–10 days [29, 31, 32]. French et al. [30] continued this treatment postoperatively in cases of immediate post-extraction implantation or simultaneous grafting; if these cases are excluded, the implant failure rate was similar between penicillin-allergic (4/403, 0.99%) and non-allergic individuals (33/4476, 0.73%).

The present findings and the results of previous research [30, 47, 48, 57, 58, 63], including the RCT by Santamaría Arrieta et al. [40], indicate that a single dose of 600 mg clindamycin before implant surgery does not increase the risk of early implant failure. However, longer postoperative treatment with clindamycin may impair osseointegration by reducing osteoblast metabolic activity and proliferation and altering the osteoimmune system. A longer clindamycin regimen may also favor the emergence of antibiotic-resistant strains and the development of postoperative infection, increasing the risk of implant failure.

These results confirm that a single dose of 600 mg clindamycin at 1 h before implant surgery is a safe antibiotic prophylactic approach; however, when a more prolonged antibiotic therapy is required, it appears advisable to prescribe an alternative antibiotic to avoid adverse effects.

The main study limitation is the sample size, although it was estimated in accordance with Wittes guidelines [35] and values published by Edibam et al. (2023) [45], among others. Given that the study may be underpowered, the results should be interpreted with due caution and need to be verified by more RCTs with wider samples.

Further studies are needed on early implant failure and postoperative infection in penicillin-allergic individuals after preoperative prophylaxis with a single dose of clindamycin, placebo, and/or other antibiotics. Such research is necessary to fully elucidate the degree to which these outcomes are attributable to chronic clindamycin exposure or to the penicillin allergy itself.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the ethical committee of the University of Granada and with the 1964 Helsinki Declaration.

Informed consent Informed consent was obtained from all individual participants in the study.

Competing interests The authors declare no competing interests.

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