



The effect of systemic antibiotics on clinical and patient-reported outcome measures of oral implant therapy with simultaneous guided bone regeneration

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Abstract

Objectives: The aim of the present superiority study was to determine the effect of systemic antibiotics primarily on patient-reported outcome measures (PROMs) and post-surgical complications in patients undergoing oral implant therapy with simultaneous guided bone regeneration (GBR).

Materials and Methods: A total of 236 medically and periodontally healthy patients received oral implants with simultaneous GBR at seven centres. Pre-operative antibiotics of 2 g amoxicillin were prescribed to the test group 1 hr prior to surgery and 500 mg thrice daily on days 1–3 after surgery. The control group was given a placebo. Group allocation was performed randomly. Primary outcome variables were PROMs recorded as visual analogue scale scores assessed on days 1–7 and 14 on pain, swelling, haematoma and bleeding. Post-operative complications as secondary outcome variables were examined at 1, 2, 4 and 12 weeks from surgery. Chi-square tests and repeated measures of analysis of variance (ANOVA) were performed for statistical evaluation.

Results: No statistically significant differences ($p > .05$) between the two groups were detected for the evaluated PROMs. The same was noted with respect to post-surgical complications. Four implants were lost—three in the test group and one in the control group.

Conclusion: In this trial, systemic antibiotics did not provide additional benefits to PROMs, nor the prevention of post-surgical complications in medically and periodontally healthy patients undergoing oral implant therapy with simultaneous GBR. However, further studies with larger sample sizes are still required to support the clinical outcomes of this study.

*See Appendix for International Team for Implantology (ITI) Antibiotic Study Group.

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KEYWORDS

biomaterials, bone regeneration, bone substitutes, drug delivery, guided tissue regeneration, patient-centred outcomes, pharmacology

1 | INTRODUCTION

The use of systemic oral antibiotics as prophylaxis against post-surgical infection in implant dentistry has been documented (Esposito, Grusovin, & Worthington, 2013). However, recommendations with regard to antibiotic prophylaxis in guided bone regeneration procedures are often based on personal and anecdotal experience (Deeb, Soung, Best, & Laskin, 2015; Suda, Henschel, Patel, Fitzpatrick, & Evans, 2017). With the increasing worldwide demand for oral implants and oral bone augmentation procedures and the development of antibiotic resistance due to indiscriminate usage, the use of antibiotics with standard oral implant therapy and GBR should be re-evaluated and proper guidelines established (Tan et al., 2014).

Furthermore, there is emerging evidence of significant long-term implications of systemic antibiotics due to disturbance of the body's microbial balance, in particular with regard to the gastrointestinal microbiota. New evidence has indicated the use of systemic antibiotics to be connected with nutrition disorders, obesity, chronic psycho-social stress-induced conditions and immune system deregulation due to major disturbance of the bacterial equilibrium of the gastrointestinal system (Rosa, Brancaglion, Miyauchi-Tavares, Corsetti, & Almeida, 2018; Vemuri et al., 2018). In light of such findings, the question of whether the potential benefit of antibiotic prophylaxis with oral implant therapy and GBR outweighs the long-term risks or even the short-term medication-related side effects such as diarrhoea, rashes or fungal infections remains to be determined. There is a long history of antibiotics being used as surgical prophylaxis to accompany the placement of dental implants, a practice that evolved due to a lack of awareness regarding the potential harmful effects of antibiotics and the growing bacterial resistance. It is therefore necessary to scrutinize the concept of routine administration of antibiotics in systemically healthy patients undergoing oral implant therapy (Park, Tennant, Walsh, & Kruger, 2018).

In the field of oral implant therapy and GBR, the use of systemic antibiotics remains a controversial issue, with various antibiotic regimes being advocated (Powell, Mealey, Deas, McDonnell, & Moritz, 2005). Some authors did not find additional benefits with the use of antibiotics when compared to controls. In two randomized controlled clinical trials (Abu-Ta'a, 2008; Tan et al., 2014), the authors found no significant advantages pertaining to post-surgical infection and complications with the use of peri-operative antibiotics for standard oral implant therapy. Also, Park et al. concluded, in a recent systematic review, that antibiotic use in healthy patients for the prophylaxis of surgical infection associated with oral implant therapy does not appear to improve clinical outcomes. They further suggested that practitioners should apply principles

of antimicrobial stewardship and not use antibiotics as a routine measure in healthy patients (Park et al., 2018). Despite ongoing multinational attempts to enforce awareness of antimicrobial resistance, the abuse of antimicrobials may in part be elicited by patient demand in a bid to avoid infections. Often, there may be a misunderstanding by patients in what signs or symptoms constitute an infection, and as such, clinicians may feel pressurized into prescribing antibiotics unnecessarily. As such, studies considering patient outcomes may be of benefit in providing evidence towards appropriate antimicrobial stewardship.

Due to a lack of randomized controlled clinical trials investigating the effect of systemic antibiotics on post-surgical complications with oral implant therapy and simultaneous GBR so far, there is no clear evidence to recommend the use of routine antibiotics to prevent infections for this indication as well.

As such, studies implicated in supporting the avoidance of excessive antibiotic usage would likely need to show no additional benefits to the effects of treatment with antibiotics as a means of proving consistency and avoidance of detrimental outcomes.

This multicentre randomized clinical trial (RCT) was designed as superiority study aiming to investigate the effect of systemic antibiotics primarily on patient-reported outcome measures (PROMs) and secondarily on post-surgical complications in medically and periodontally healthy patients undergoing oral implant therapy and simultaneous GBR. The null hypothesis tested was that there were no differences in PROMs following treatment and post-surgical complications between the two groups tested.

2 | MATERIAL AND METHODS

This study was initiated as a subsequent study to the paper published by Tan et al. (2014), which explored the effects of antibiotic intervention on conventional oral implant therapy. As a development of that investigation, this study aimed to consider how the addition of GBR may affect these post-surgical outcomes—where in the original paper simple implant placement heralded no impact whatsoever on both PROMs nor post-surgical complications.

2.1 | Subject population

The following seven study centres belong to the Antibiotic Research Group and were included as part of the multicentre trial:

1. Department of Oral Surgery and Orthodontics, Graz Austria, Medical University Graz, University Clinic of Dental Medicine & Oral Health;

2. National Dental Centre Singapore, Singapore;
3. Peking University, School of Stomatology, Beijing PR China;
4. Griffith University, Gold Coast, School of Dentistry and Oral Health, Queensland, Australia;
5. The University of Hong Kong, Faculty of Dentistry, Hong Kong SAR PR China;
6. University of Iceland, Faculty of Odontology, Reykjavik, Iceland; and
7. Shanghai Jiao Tong University, Shanghai Ninth People's Hospital, Department of Implant Dentistry, Shanghai PR China

Subjects were recruited across all centres, between August 2014 and September 2017.

The study protocol was submitted to and approved by the respective institutional review boards of the seven institutions. Subjects were screened consecutively and selected through regular implant assessment clinics by calibrated examiners at each centre. Patients that were enrolled fulfilled the following inclusion criteria:

- Medically healthy with no known allergy to amoxicillin or penicillin antibiotics and/or starch.
- No administration of any form of antibiotics in the last 6 months.
- Non-smoker or light smoker or a previous smoker who had quit for 5 years or more.
- Periodontal health, as confirmed by clinical examination (Heitz-Mayfield, Needleman, Salvi, & Pjetursson, 2014; Matuliene et al., 2008).
- Edentulous space (up to 3 units), with a horizontal bone defect suitable for implant placement with simultaneous GBR—in cases requiring multiple implant placement, one study implant was selected randomly after surgery and included for further study assessments.

Medical health was assessed with the help of standardized health questionnaires. Study enrolment was limited to subjects aged ≥ 21 years with a score of 1 or 2 according to the physical status classification of the American Society of Anesthesiologists (ASA) (Mak, Campbell, & Irwin, 2002).

Medically compromised subjects (ASA classification III-V), general contraindications against implant treatment or augmentative procedures (e.g. immunodeficiency, advanced systemic diseases, corticosteroid medication), and treatments or diseases that may have an effect on bone turnover or bone or non-mineralized tissue metabolism (e.g. bisphosphonates or local radiotherapy) were reasons for exclusion from the study.

Periodontal and radiographic examinations were performed including assessment of probing depth (PD) and Bleeding on Probing (BOP). Further, full-mouth bleeding scores and full-mouth plaque scores were obtained.

Only patients with PD < 5 mm without concomitant bleeding, full-mouth bleeding score and full-mouth plaque score of $< 20\%$ were included in order to reduce the risk of subsequent biological complications such as peri-implantary and periodontal infections

as described by Matuliene and co-workers and Heitz-Mayfield and co-workers (Heitz-Mayfield et al., 2014; Matuliene et al., 2008).

Furthermore, the dimensions of the edentulous sites were analyzed with the help of two and if necessary three-dimensional radiographs in order to ensure suitability for a simultaneous surgical protocol prior to the intervention.

The included cases were considered as “advanced” according to the Straightforward/Advanced/Complex (SAC) classification in implant dentistry (Dawson et al., 2009) allowing implant placement and simultaneous GBR as described by Hämmerle and co-workers (Hämmerle, Chiantella, Karring, & Lang, 1998).

All patients were fully informed regarding the purpose of the study and the risks and benefits associated with participation. Signed informed consent was obtained by all patients.

2.2 | Investigator training

The study was designed as RCT, with two arms (one test group and one control). The examiners and patients were blinded. Prior to the commencement of the study, a whole day investigator and examiner training was held during the ITI World Congress in 2014 in Geneva: Each centre sent one representative centre coordinator to participate in the training and who would manage the further internal training (surgeons, examiners and patients) at the different centres. Up to four surgeons were allowed to perform the clinical procedures in each centre, but only one could be enrolled as the clinical examiner.

For both clinical examiners and surgeons, all relevant steps were outlined by M.P., N.P.L. and N.M. in oral and with the help of a Microsoft® PowerPoint® presentation (ppt®) (Microsoft, Redmond, USA). The instructions during the training were given in chronological order based on the study protocol; this included pre-treatments, patient selection, periodontal examination, intraoperative steps, study medication, post-operative assessments and complication management. At the end of the meeting, the ppt® presentation was handed over to the participants of the meeting to be used for further training at their centre. The further centre screenings were performed in a consecutive manner in meetings in 2016, 2017 and 2018. Again, one representative of each centre was present at the meetings to report on the current status of the investigation at each centre. Although all investigators were trained in the study proceedings, they may not be considered properly calibrated.

2.3 | Clinical procedures

A list of randomized allocation with block size of 4 was generated for each of the centres by a statistician not involved in the clinical procedures and data collection. Patients recruited were randomized to the test and control groups following the randomized allocation.

The study medication was prescribed by a designated clinical coordinator from the centre, who was not involved as a surgeon or examiner. The surgeons involved had no access to the data collection

sheets or the group allocation, whilst the examiner had no access to the patients' treatment notes or group allocation. Randomization was performed at the time of consent owing to the fact that the test and the control groups had to take the medication prior to implant placement.

2.4 | Study medication

The placebo and test products were prepared, identically packed and numbered in a certified laboratory (Allerheiligen Apotheke Herbert Baldia KG, Vienna, Austria) and distributed to the study centres. The centres were not aware of the medication codes.

Two hours prior to surgery, each subject received a box with a numbered code (according to group allocation but not readable for the patient; all containers were unmarked but identical) containing medication or placebo with a detailed written instruction on timing and dosage of consumption of the medication/placebo on top. Additionally, a verbal instruction was performed by the person performing surgery (different to the blinded examiner responsible for the assessment of clinical parameters).

- In the test group, pre-operative administration of 2 g amoxicillin (Moxilen® Medochemie, Cyprus) 1 hr prior to implant placement and GBR was administered. An additional single dose of 500 mg of amoxicillin was given 8 hr after surgery and 500 mg thrice daily (8 hourly) on days 1–3 following implant placement and GBR.
- In the control group, a pre-operative placebo (containing corn starch) of 2 g was administered. An additional single dose of 500 mg of placebo was administered 8 hr after surgery and 500 mg thrice daily (8 hourly) on days 1–3 following implant placement and GBR.

2.5 | Surgical protocol

Each patient rinsed for 1 min with 0.2% chlorhexidine prior to surgery. Aseptic isolation of the operative field was ensured. After local anaesthesia, a crestal incision was performed and complimentary mesial or distal releasing incisions were utilized if needed in order to reflect a full-thickness flap and expose the full margins of the bone defect.

The bony dimensions (bucco-lingual width of alveolar bone/buccal bony plate thickness and mesio-distal width of alveolar bone) of the surgical site were clinically recorded during surgery with the help of a calliper and the soft tissue flap thickness record with a University of North Carolina 15 probing instrument.

Osteotomies were carried out to the length and diameter of the implants indicated—Straumann Standard Plus® or Straumann Bone level®—Sand-blasted Long grit Acid-etched implants of diameters 3.3, 4.1 and 4.8 mm and 8–12 mm in the length (Straumann AG).

The simultaneous bone augmentation procedures were carried out using bovine hydroxyapatite (Bio-Oss®, 0.5 g/0.25–1 mm particle size, Geistlich, Wolhusen, Switzerland) and resorbable collagen membranes (Bio-Gide®; Geistlich). Special care was taken to achieve tension-free wound closure for either submerged or transmucosal healing using monofilament sutures, and horizontal periosteal release incision in the apical margin of the flap was utilized if needed, by means of a partial-thickness dissection. After surgery, intraoral baseline radiograph and post-operative occlusal photographs were taken. All groups were advised to take analgesics (paracetamol) thrice daily for two days after surgery and asked to document their intake. Patients were further instructed to use a 0.2% chlorhexidine mouth rinse twice daily for 2 weeks. One week after surgery, sutures were removed and post-operative occlusal photographs were taken.

2.6 | Clinical measurements

Dichotomous measurements Yes/No (Y/N) for pain, swelling, implant stability, purulent discharge and flap closure were collected by one blinded examiner in each centre at 1, 2, 4 and 12 weeks after the surgery. The clinical examiner was not involved in the surgical procedure and blinded to the antibiotic group allocation.

2.7 | Patient-reported outcome measures

All patients filled a set of visual analogue scale (VAS) forms for the assessment of four healing parameters pain, swelling, haematoma and bleeding over the first two post-operative weeks. Each parameter was expressed by a 10 cm VAS extending from 0 (e.g. no swelling) to 10 (e.g. very severe swelling). Patients were requested to express the level of each parameter as they experience it every day by indicating a mark along the VAS. Compliance in completing the records of VAS and analgesic consumption forms was monitored at the follow-up visits.

For the submerged implants, second-stage surgery was performed 12 weeks after implant placement and a healing abutment inserted.

Impressions were taken 12 (for the non-submerged) and 14 weeks (for the submerged) after implant placement, and 7–14 days later, single-tooth crowns were inserted onto the implants.

2.8 | Statistical analysis

Primary outcome variables of the study were PROMs as recorded in the VAS scores (0–10) assessed on days 1–7 and 14 on pain, swelling, haematoma and bleeding.

Secondary outcome variables were the presence of post-surgical complication pain, swelling, implant stability, purulent discharge and

flap closure assessed by clinical examination in a dichotomous manner at 1, 2, 4 and 12 weeks.

Chi-square (or chi-square exact) tests were used to compare the percentage distribution of post-surgical complications at weeks 1, 2, 4 and 12 between the test and control groups. Student's *t* tests and Mann–Whitney *U* tests were used to compare the mean and median VAS scores of the PROMs, respectively, at day 14 between the test and control groups. Repeated-measures ANOVA was performed on the VAS scores of the PROMs with the use of multivariate tests (Wilks' lambda) for the effect of time and the interaction effect between treatment groups and time (all effects considered to be fixed). The above analyses were performed using SPSS®. To adjust the possible centre effect, a random effect for centre (different centres considered to be a random sample of centres) was added to the above repeated-measures ANOVA using SAS®. The centre effect was evaluated when performing repeated-measures ANOVA for PROMs.

2.9 | Sample size

Sample size estimation was calculated based on a superiority trial, using software G*Power® version 3.1.9.2. The standard deviations of the PROMs based on the Tan et al. (2014) study were mostly ranged from 1.0 to 2.0. An effect size of 0.40 (moderate effect) in the differences in the mean VAS scores of the PROMs between the test and control group was considered to be of clinical importance. This corresponded to a minimum important difference of 0.4 to 0.8 in mean VAS scores. With this consideration, the required sample size would be 100 for each group when the level of significance was set at 0.05 (2-sided test) and power to be 80%. Accounting for a dropout rate of 10%, a minimum of 110 patients per group were planned for recruitment.

3 | RESULTS

Altogether, 253 data entries in the raw data file were received from the seven study centres: 17 primarily included cases had to be excluded due to heterogenous reasons such as unknown allergies/sensitivities towards the study medications (placebo or amoxicillin), lack of compliance with study appointments or incomplete/unreproducible data completion. Thus, a total of 236 cases were analysed—117 patients in the test group and 119 patients in the control group (Table 1). No significant differences (all $p > .05$) in patient profile among the two treatment groups in terms of age, gender and implant dimensions could be observed (Table 2).

The surgical procedures of all 236 subjects were uneventful. Four implants were lost—three in the test group and one in the control group. This reveals an overall implant survival rate of 98.3% for all study implants, 97.4% for implants in the test group and 99.2% for implants in the control group. There were no statistically significant differences in implant survival rate between the test and control groups ($p > .05$).

TABLE 1 Recruitment of patients at seven study centres (T = test group/C = control group)

Centre	Group		Total
	C	T	
1	12	12	24
2	27	24	51
3	20	21	41
4	11	9	20
5	10	10	20
6	26	27	53
7	13	14	27
Total	119	117	236

3.1 | Use of analgesics

The percentage of patients who took analgesics did not differ significantly ($p > .05$) between the two treatment groups over the post-operative observation period (Table 3).

3.2 | Patient-reported outcome measures

There were no statistically significant differences in the mean and median VAS scores of bleeding, swelling, pain and haematoma between the two treatment groups at day 14 (all $p > .05$). Results from the repeated-measures ANOVA confirmed that there were no statistically significant differences between the two treatment groups for bleeding, swelling, pain and haematoma (all $p > .05$; Figures 1–4). However, there was a significant time effect, where the mean VAS scores decreased over time ($p < .001$). No significant interaction effect between the treatment groups and time suggested that the decrease in the mean VAS scores in different treatment groups was not significantly different from each other for all the variables assessed.

When adjusted for the centre effect, there was a significant centre effect ($p < .001$); that is, different centres were having different mean VAS scores mainly in the first few days. For example, Centre 4 had higher mean VAS scores in bleeding than Centre 5 from day 1 to day 3, but since day 4, no significant difference could be detected any more.

3.3 | Post-surgical outcomes

Thirteen cases had incomplete post-surgical outcome. However, data from 113 patients in the test group and 110 patients in the control group were analysed. There were no statistically significant differences in flap closure, pain, swelling, pus and implant stability of the operation site between the two treatment groups at any time ($p > .05$; Table 4).

TABLE 2 Baseline characteristics of the subjects and clinical parameters in different groups (T = test group/C = control group)

	C (n = 119)	T (n = 117)	Total (n = 236)	p-Value
Age (Mean)	44.8	47.2	46.0	.196
Gender (%)				
Male	55.5	50.4	53.0	.438
Female	44.5	49.6	47.0	
Diameter of the implants used (%)				
3.3 mm	32.8	32.5	32.6	.699
4.1 mm	47.0	51.3	49.2	
4.8 mm	20.2	16.2	18.2	
Length of the implants used (%)				
8 mm	11.8	5.1	8.5	.159 ^a
10 mm	58.0	70.1	64.0	
12 mm	26.9	22.2	24.6	
14 mm	3.3	2.6	2.9	

^aChi-square exact test.

TABLE 3 Percentages of subjects who took analgesics (n = 236) (T = test group/C = control group)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14
C (n = 119)	47.9	46.2	36.8	26.7	18.8	16.2	9.3	4.2
T (n = 117)	46.2	36.8	30.8	20.7	16.4	11.4	6.3	2.6
Total	47.0	41.5	33.8	23.7	17.6	13.9	7.8	3.4
p-Value	.793	.144	.333	.280	.627	.287	.386	.722 ^a

^aChi-square exact test.

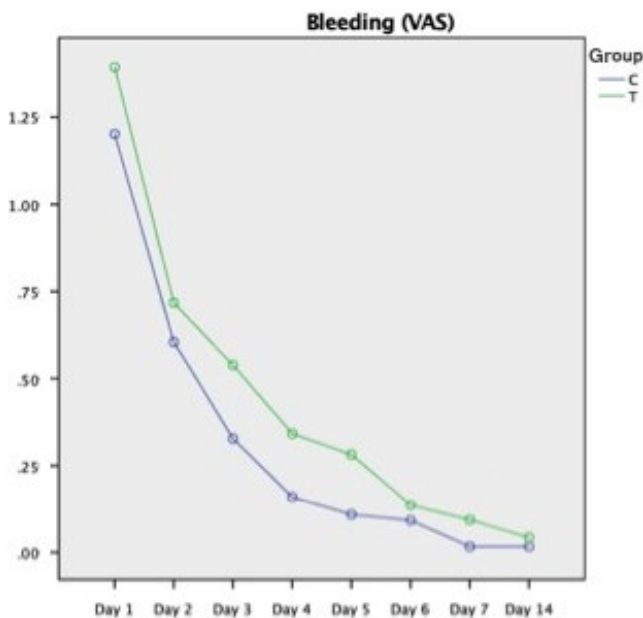


FIGURE 1 Mean ± SD (standard deviation) visual analogue scale (VAS) of bleeding (Bleeding-VAS) from day 1 to day 14. (T = test group/C = control group)

4 | DISCUSSION

The present study was aiming to determine the effect of systemic antibiotics on PROMs and post-surgical complications in patients

undergoing oral implant therapy with simultaneous GBR. In this instance, PROMs of 236 cases—117 patients in the test group and 119 patients in the control group—were assessed as primary outcome measures relating to pain, swelling, bleeding and haematoma. Results from the repeated-measures ANOVA revealed no statistically significant differences between the two treatment groups.

As secondary outcome variable of this study, the evaluation of data from 113 patients in the test group and 110 patients in the control group for the assessment of post-surgical complications showed no statistically significant differences in flap closure, pain, swelling, pus and implant stability of the operation site between the two groups.

It could be argued that the absence of significant differences in the secondary outcome variables in this trial might be due to the low prevalence of post-surgical complications, and therefore, the study might not have enough power to find the existence of difference for these outcomes. However, although there were no statistically significant differences in post-surgical complications, clinically differences, for example in regard to suppuration, which was greater in the control group, could influence clinical behaviours with regard to the prescription of systemic antibiotics.

Beyond the administration of antimicrobials, analgesic consumption was documented in the present trial and was higher in the control group from day zero until day 14 after surgery. Again, the difference was not statistically significant; however, clinical interpretation of this outcome may be different in general practice setting.

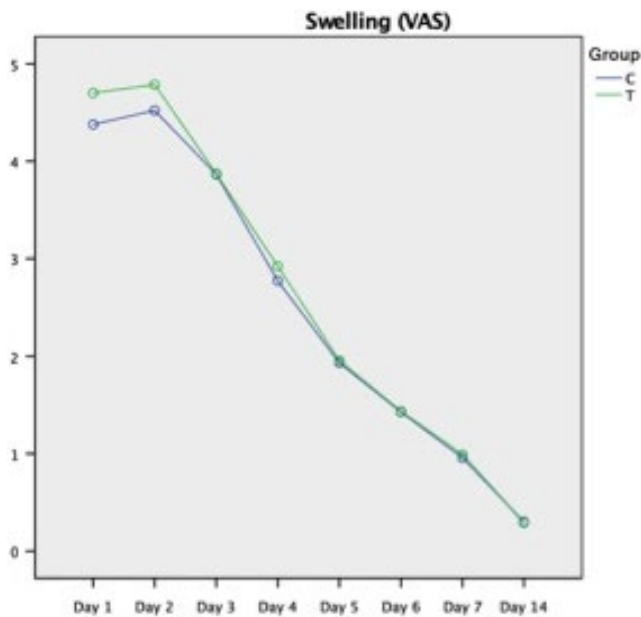


FIGURE 2 Mean \pm SD (standard deviation) visual analogue scale (VAS) of swelling (Swelling-VAS) from day 1 to day 14. (T = test group/C = control group)

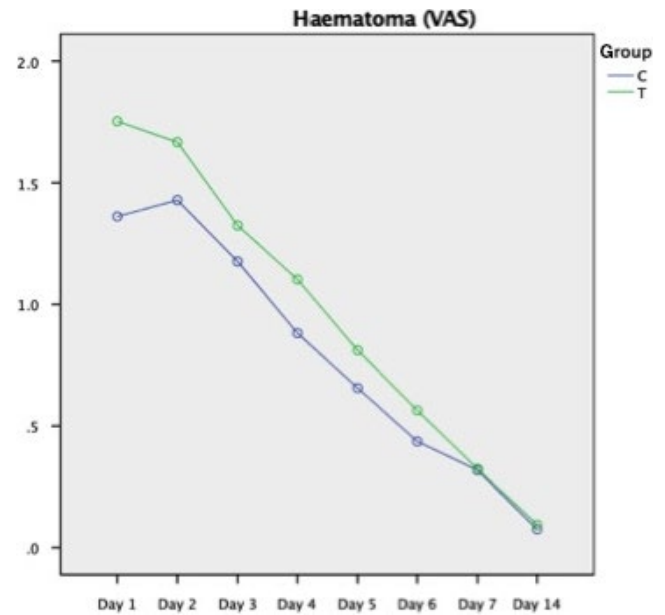


FIGURE 4 Mean \pm SD (standard deviation) visual analogue scale (VAS) of haematoma (Haematoma-VAS) from day 1 to day 14 (T = test group/C = control group)

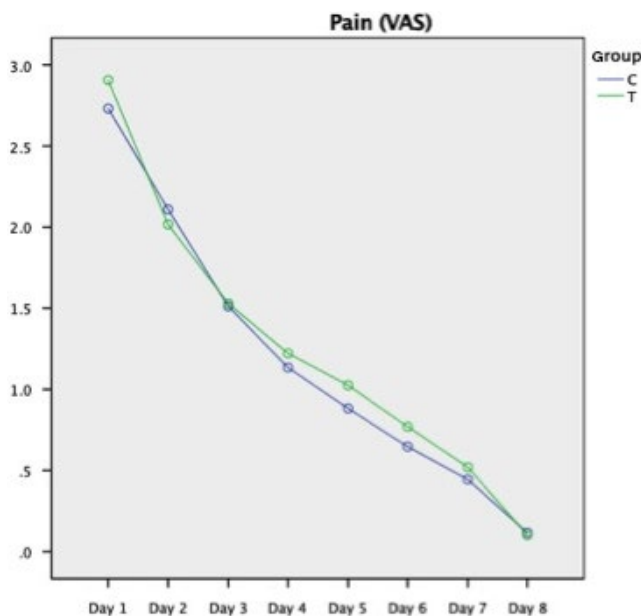


FIGURE 3 Mean \pm SD (standard deviation) visual analogue scale (VAS) of pain (Pain-VAS) from day 1 to day 14 (T = test group/C = control group)

In the present trial, a total of four out of 236 implants were lost—three in the test group receiving oral antibiotics and one in the control group without antibiotic prophylaxis. This corresponds to an overall implant survival rate of 98.3% for all study implants, 97.4% for implants in the test group and 99.2% for implants in the control group. Survival rates are in accordance with those of other studies and show no statistically significant difference between the two treatment groups (Jemt, 2018).

Since implant survival (incorporation rate) is very high in today's clinical practice, most of the studies addressing this parameter in relation to peri-operative antibiotic prophylaxis must be considered as underpowered (Esposito, Grusovin, Loli, Coulthard, & Worthington, 2010). Only the meta-analysis of four underpowered studies (Abu-Ta'a et al., 2008; Anitua et al., 2009; Esposito, Cannizzaro, et al., 2010; Esposito et al., 2008) revealed a risk ratio of 0.4 (95% Confidence Interval: 0.19–0.84) for early implant failures. As indicated above, these implant failures cannot be taken as evidence of the beneficial effect of peri-surgical prophylactic antibiotics, owing to the presumptive surgical confounders. In the meta-analysis of the four studies mentioned, the risk ratio for post-surgical infection was 0.74 (95% CI: 0.37–1.47). In this relevant parameter for the effect of peri-operative antibiotic administration, statistical significance was not reached indicating a lack of benefit from the antibiotic regimes.

In the following systematic Cochrane review including six RCTs (1,162 patients) by Esposito et al., the authors concluded antibiotics to be beneficial for reducing failure of dental implants placed in ordinary conditions. Specifically, a single oral administration of two or three g one hour pre-operatively seemed to reduce failure of dental implants (Esposito et al., 2013).

However, it is crucial to be aware that this Cochrane review considered implant failures as a specific point of assessment rather than PROMs. It is also worth considering the studies included in this review maintained similar clinical standards to this paper (such as systemic and periodontal health), and several followed similar peri-operative protocols, for example the use of chlorhexidine rinse (Anitua et al., 2009; Caiazzo, Casavecchia, Barone, & Brugnami, 2011; Esposito, Cannizzaro, et al., 2010; Esposito et al., 2008; Esposito, Grusovin, et al., 2010). Nonetheless, there were notable variations in protocols, such as in the paper by Nolan and

TABLE 4 Percentages of subjects with post-surgical outcome variables in the different groups at weeks 1, 2, 4 and 12 after surgery (T = test group/C = control group)

	C (n = 110)	T (n = 113)	Total (n = 223)	p-value
Flap closure				
1 week	83.6	87.6	85.7	.397
2 weeks	82.7	77.9	80.3	.363
4 weeks	90.0	84.1	87.0	.188
12 weeks	83.6	84.1	83.9	.930
Pain				
1 week	30.0	26.5	28.3	.567
2 weeks	10.9	10.6	10.8	.944
4 weeks	8.2	3.5	5.8	.139
12 weeks	2.7	0.9	1.8	.365 ^a
Swelling				
1 week	42.7	38.9	40.8	.565
2 weeks	13.6	18.6	16.1	.315
4 weeks	2.7	2.7	2.7	1.000 ^a
12 weeks	0.9	1.8	1.3	1.000 ^a
Pus				
1 week	3.6	1.8	2.7	.442 ^a
2 weeks	1.8	0.9	1.3	.618 ^a
4 weeks	0.9	0.9	0.9	1.000 ^a
12 weeks	1.8	0.0	0.9	.242 ^a
Implant stability				
1 week	99.1	100.0	99.6	.493 ^a
2 weeks	99.1	100.0	99.6	.493 ^a
4 weeks	98.2	97.3	97.8	1.000 ^a
12 weeks	99.1	97.3	98.2	.622 ^a

^aChi-square exact test.

co-workers where no post-operative medication was prescribed to either group and in Anitua et al. where a preparation rich in growth factor (PRGF) was included in the operative protocol and post-operative steroids, which could have impacted post-operative healing patterns (Anitua et al., 2009; Nolan, Kemmoona, Polyzois, & Claffey, 2014).

Furthermore, work by Esposito and co-workers explored antibiotics in treatment outcomes but only compared test and placebo groups in the pre-operative setting and included a large variety of implant procedures; results noted no statistically significant differences between either group (Esposito, Cannizzaro, et al., 2010).

It should be noted that both in the preceding trial by Tan et al. and in this study, the administration of pre-, peri- or post-surgical prophylactic antibiotics did not influence the wound healing pattern, the subjective variables nor general implant survival at all (Tan et al., 2014). This may be as a result of the high standards of infection control expected of the implant surgical procedures at all the centres participating in this study. Further, all included patients had been treated periodontally prior to implant installation.

In spite of differences in PROMs between the centres, consistent overall results were obtained. However, in this context it should be mentioned that the sample size calculation expected to detect

differences in the outcomes only with 100 subjects required per arm. As no centre reached that figure, no statistically significant differences could be expected.

In the present study, no technical complications were diagnosed within the observation period irrespective of the group allocation of the patients. This may be due to the fact that only one implant system was used, thus minimizing the various possibilities of technical complications.

On the other hand, biological complications (peri-implant mucositis, peri-implantitis) have to be considered as generic and not related to implant systems (Abrahamsson, Berglundh, & Lindhe, 1998; Albouy, Abrahamsson, Persson, & Berglundh, 2008, 2009). In addition, to minimize further confounding factors only one bone substitute and type of barrier membrane were used in this trial.

When interpreting the results of this trial, it has to be considered that only subjects with defects allowing simultaneous implant insertion and GBR were admitted. Therefore, no statement on the necessity of antibiotic prophylaxis during treatment of highly atrophic sites in a staged approach can be made. The included cases were considered as "advanced" according to the SAC classification in implant dentistry (Dawson et al., 2009) allowing a simultaneous fixture placement and grafting approach.

The broad-spectrum antibiotic used was amoxicillin (Moxilen® Medochemie, Cyprus), a well-documented semi-synthetic analogue of ampicillin, derived from the basic penicillin nucleus (6-aminopenicillanic acid) providing a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms (Suda et al., 2017). It is, however, susceptible to degradation by β -lactamases, and therefore, its spectrum of activity does not include organisms producing these enzymes. Nevertheless, amoxicillin was chosen as the antibiotic of choice in this study as it is considered a suitable first-line agent, demonstrating a high level of antimicrobial activity in patients with dento-alveolar infections (Kuriyama et al., 2007).

The pre-operative dosage of amoxicillin applied in the preceding study published by Tan et al. was based on the antibiotic dosage recommendation by the American Heart Association (AHA) for prevention of infective endocarditis (Wilson et al., 2007).

In subjects with increased systemically risk factors, such as antiresorptive therapy, successful implant therapy is feasible—however, an individual risk assessment taking the primary disease and medication(s) into account with regard to further compromise to wound healing seems mandatory. Walter and co-workers further concluded that in these types of compromised patients, bone augmentations should be avoided, and peri-operative antimicrobial prophylaxis is highly recommended (Walter, Al-Nawas, Wolff, Schiegnitz, & Grötz, 2016).

In conclusion, it appears that systemic antibiotics do not provide any improvement in PROMs in healthy patients undergoing oral implant therapy and simultaneous GBR in comparison with a placebo group. Furthermore, between the two groups tested, there was also no significant reduction in post-surgical complications. However, it is crucial to remember that underpowering must be considered when interpreting the clinical outcomes of this trial.

To what extent antibiotics may be indicated to improve PROMs for complex staged or other wide-ranging implant procedures, such as sinus augmentation procedures, remains to be explored in future trials of the study group.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

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