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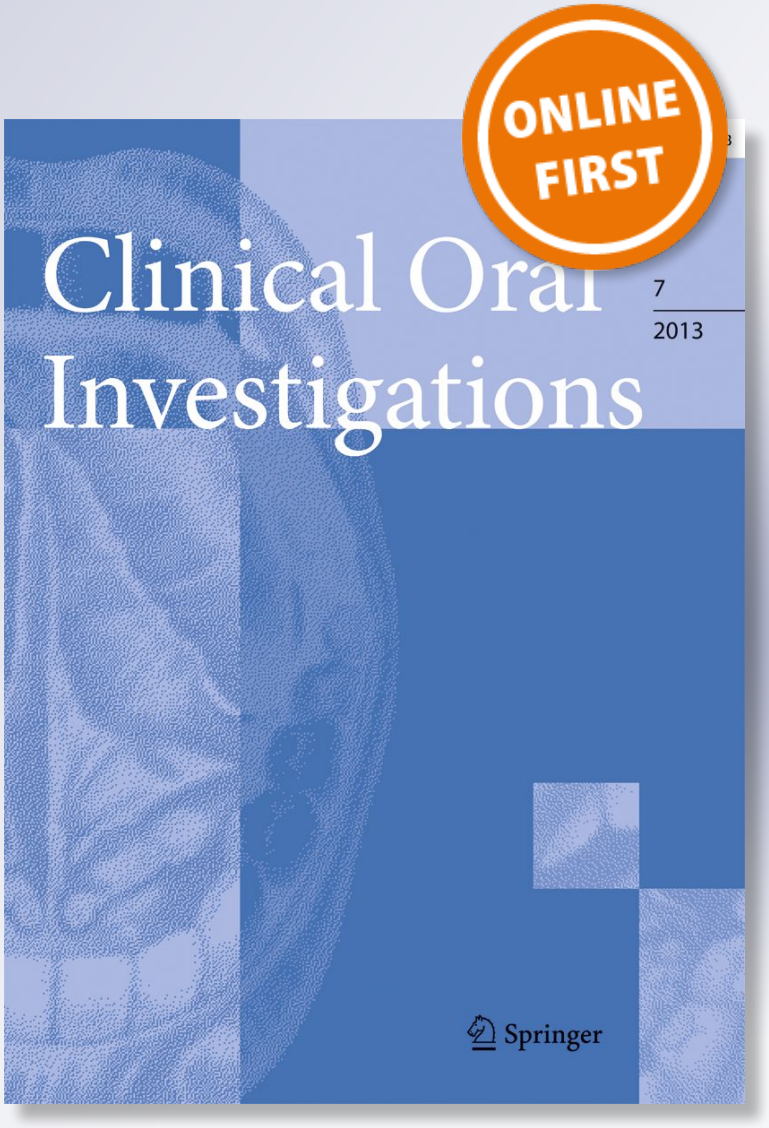

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ORIGINAL ARTICLE

Vancomycin and tobramycin impregnated mineralized allograft for the surgical regenerative treatment of peri-implantitis: a 1-year follow-up case series

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Abstract

Objectives To assess the clinical and radiographic outcomes of the regenerative treatment of peri-implantitis using a vancomycin and tobramycin impregnated allograft (VTA) after a 12-month period.

Material and methods Thirteen consecutive patients who required a regenerative treatment of peri-implantitis were recruited. For the 17 implant sites, a flap was raised, and after mechanical and chemical implant decontamination, a vancomycin and tobramycin impregnated allograft was placed in the defect and then covered with a collagen membrane. Soft tissues were sutured allowing a non-submerged healing. Clinical and radiographic variables were evaluated at baseline and at 12 months after treatment.

Results No signs of continuous bone loss were observed and no implant was lost, yielding a 100% survival rate. All patient's clinical examination at 12 months revealed peri-implant health showing absence of suppuration and a statistically significant reduction in terms of bleeding on probing scores (70.6%, $P = 0.001$). Initial probing pocket depth (7.88 ± 1.22 mm) was significantly reduced at 12 months healing, a mean reduction of 4.23 ± 1.47 mm ($P = 0.001$) was achieved. The mean radiological infrabony defect at baseline reached 4.33 ± 1.62 mm, and was significantly reduced up to 0.56 ± 0.88 mm, which represents an 86.99 ± 18.2% bone fill from the original infrabony defect.

Conclusions Within the limits of the study, the application of VTA with a collagen membrane yielded positive outcomes in terms of radiographic bone fill, pocket depth reduction, and attachment gain after a 12-month period. Thus, VTA plus a collagen membrane seem to be suitable for the regenerative treatment of peri-implantitis.

Clinical relevance The use of locally delivered antibiotic together with the bone graft may reduce the undesirable effects related to the systemic administration and the risk of resistances. In the light of the results obtained, these grafting materials might offer new treatment strategies in the surgical regenerative treatment of peri-implantitis.

Keywords Peri-implantitis · Surgical treatment · Regeneration · Allograft · Local antibiotic · Antibiotic

Introduction

Peri-implantitis is an inflammatory disease characterized by loss of supporting bone surrounding the implant [1]. The consensus indicates that changes in probing depth, the presence of bleeding on probing, and suppuration must be evaluated to assess the peri-implant tissues, while radiographs should be used to confirm peri-implant bone loss [2]. Although the current epidemiological data are limited, peri-implant mucositis has been reported to affect up to 42.2% of the patients while peri-implantitis affects 21.7% of the population [3].

The primary objective for the treatment of peri-implantitis is to remove the biofilm from the implant surface to a degree that healing and health can occur. In the past years, several treatment modalities, such as mechanical debridement, resective surgery, or regenerative procedures with chemical conditioning of the implant surface, have been used to arrest disease progression and restore the peri-implant tissues [4, 5]. Animal studies demonstrated that the use of bone substitutes with or without the use of a membrane on decontaminated implant surfaces achieved different amounts of re-

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osseointegration [6, 7], although discordant results were reported [8].

In spite of mechanical debridement and disinfection of implant surfaces are able to remove the oral biofilm and periodontopathogenic microbes to some extent, an absolute extermination of the oral biofilm is difficult to accomplish because of variations in surface characteristics and the morphology of the various implant systems [9]. It is hypothesized that local or systemic delivery of antibiotics in combination with mechanical peri-implant treatment could eliminate bacteria to a greater extent compared with mechanical therapy performed alone, improving the treatment results of peri-implantitis [10].

To determine the type of antibiotic, route of administration, dosage, and duration of use, it is needed to analyze the peri-implant microbiology. The microbiota associated with peri-implant diseases is a mixed anaerobic infection, with a composition similar to that of the subgingival microbiota of chronic periodontitis [11]. Nevertheless, a number of microorganisms have been identified in peri-implantitis that are not common in periodontitis. These include bacterial species such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Helicobacter pylori*, *Peptostreptococcus micra*, *Pseudomonas spp.*, as well as *Candida spp. fungi* [12]. Furthermore, patients with peri-implantitis yielded submucosal bacterial pathogens resistant in vitro to individual therapeutic concentrations of clindamycin, amoxicillin, doxycycline, or metronidazole, these are most often *Prevotella intermedia/nigrescens* or *Streptococcus constellatus* [11]. If generally administered, many antibiotics have only limited penetration into bone tissue, for instance in case of beta-lactam antibiotics, it is only 10 to 20% of serum concentrations [13]. The probability of treatment failure then rises if exists lower sensitivity of microorganism, or apparent resistance to antibiotic administered.

Some investigations showed that an alternative to increase the therapeutic potential of antibiotics and reduce the impact of unfavorable development of antibiotics resistance might be the use of local delivery antibiotics [14]. Vancomycin and tobramycin have already been used locally along with bone regeneration in orthopedics [14]. Vancomycin belongs to the glycopeptide group, and it is chosen because of its spectrum of antibacterial activity, covering all Streptococcus strains such as *beta haemolytic Streptococcus*, *Streptococcus viridans*, *Streptococcus pneumoniae*, and *Streptococcus aureus*, as well as aerobic and anaerobic gram-positive cocci and rods [15–16]. Levels of vancomycin range above minimum inhibitory concentration (MIC) even after 16 days, inhibiting not only sensitive staphylococci (MIC < 2 mg/l), but even staphylococci with limited sensitivity to vancomycin (Vancomycin-Intermediate *Staphylococcus Aureus* (VISA), MIC: 4–8 mg/l) [17]. On the other hand, tobramycin is a widely used aminoglycoside. It is a bactericidal antibiotic, effective against many gram-negative pathogens, and it is also considered more active than gentamicin against *Pseudomonas aeruginosa*. It also presents a low resistance rate and allergy rate [18, 19].

Thus, the combination of these two locally delivered antibiotics may provide a spectrum of antimicrobial activity covering most of the species involved in peri-implantitis, reducing the undesirable effects related to systemic administration and antibiotic resistance.

Hence, the aim of the present evaluation was to assess in a case series the clinical and radiographic outcomes of a regenerative approach using an allograft bone impregnated with vancomycin and tobramycin in the treatment of peri-implantitis lesions after a healing period of 12 months.

Material and methods

Patient population

This prospective case series was performed in a private practice from January 2012 until December 2014. Consecutive patients suffering from advanced peri-implantitis who needed to be scheduled for regenerative therapy of a peri-implant infrabony defect were included.

Each patient had at least one implant with two-wall or three-wall infrabony defects ≥ 3 mm of depth identified on intraoral radiographs, in association with a probing pocket depth > 5 mm with bleeding on probing and/or suppuration. Implant sites need to be surrounded by a minimum of 2 mm of keratinized gingiva. Furthermore, the following inclusion criteria were considered: (1) age ≥ 18 years; (2) treated chronic periodontitis, based on the current classification of the American Academy of Periodontology [20]; (3) full-mouth plaque score < 25%; (4) full-mouth bleeding score < 25%; and (5) cemented and screw-retained single-unit crowns and partial dental prosthesis. Patients were excluded on the basis of: (1) implant mobility; (2) radiographic peri-implant bone loss > 50%; (3) pregnancy or lactating females; (4) any medical condition which contraindicated dental surgery; (5) systemic diseases, medications, or conditions that may compromise wound healing and influence the outcome of the therapy; (6) known allergy to vancomycin or tobramycin; (7) use of systemic antibiotics during the previous 3 months; (8) use of systemic antibiotics for endocarditis prophylaxis; and (9) smoking more than 10 cigarettes/day. Subjects smoking < 10 cigarettes per day were requested to stop smoking before and after the surgical procedure.

This case series study was performed in accordance with the Universitat Internacional de Catalunya ethical committee (PERECL201702) and Helsinki Declaration. All patients read and signed an appropriate informed consent document prior to participation in the study.

Pre-surgical procedures

Before the surgical procedure, all patients received extensive oral hygiene instructions and underwent non-surgical periodontal therapy consisting of supra- and subgingival mechanical debridement. When implant-supported prosthesis did not allow access for proper oral hygiene corrections were performed at baseline. Four to 6 weeks after completion of the non-surgical therapy, a clinical reevaluation was performed and this time point was considered the baseline (Fig. 1a, b).

Surgical treatment

All surgeries were performed by one experienced periodontist (JN), and in order to facilitate surgery access, screw-retained crowns were removed. After local anesthesia (articaine 4% and adrenaline 1:100,000), a mucoperiosteal flap was raised by means of intracrevicular incisions in order to expose both the labial and palatal/lingual aspects of the affected implants. Incisions were designed to preserve as much of the interproximal tissue as possible. Subsequently, all granulation tissue was completely removed from the defect using stainless steel curettes (Hu-Friedy®, Rockwell St, Chicago, IL). The supracrestal component of the defect was treated with implantoplasty beginning with a diamond bur of 40- and 15-μm grit size (Komet dental, Brasseler,® Germany) and ending up with the Arkansas stone (Komet dental, Brasseler,® Germany) [21]. The implant surface located in the intrabony defect was carefully debrided with an ultrasonic device (DTE-D5, Woodpecker®, Guilin, China) and treated with hydrogen peroxide (3%) for 1 min. Then, the implant surface and the adjacent alveolar bone were rinsed with copious amounts of saline (Fig. 1c). The intrabony component was filled with a mixture of 50% of a particulate mineralized cancellous allograft impregnated with vancomycin (OSTEOmycin V®, European Cell and Tissue Bank, Wels, Austria) and 50% of a particulate mineralized cancellous allograft impregnated with tobramycine (OSTEOmycin T®, European Cell and Tissue Bank, Wels, Austria) (Fig. 1d). A cross-link collagen membrane (Ossix Plus®, Datum Dental Ltd., Lod, Israel) was trimmed to completely cover the entire defect and extend 2 mm over the surrounding alveolar bone (Fig. 1e). The graft material and membrane were hydrated in sterile saline prior to application. Finally, the flaps were repositioned and sutured with non-resorbable polytetrafluoroethylene (PTFE) (5–0 Cytoplast®; Osteogenics Biomedical INC., Lubbock, TX, USA) interrupted single sutures (Fig. 1f). The wound healing was performed in a non-submerged mode.

Postoperative care

Subjects were instructed to avoid mechanical hygiene procedures at the treated sites and to rinse with a 0.12% chlorhexidine digluconate solution (Perio-Aid®, Dentaid, Barcelona, Spain) twice a day until suture removal. After surgery, ibuprofen 600 mg was prescribed three times per day if needed. Sutures were removed 7–14 days after surgery and the patients were re-instructed to use a soft toothbrush after the first week of healing. Recall appointments were performed every

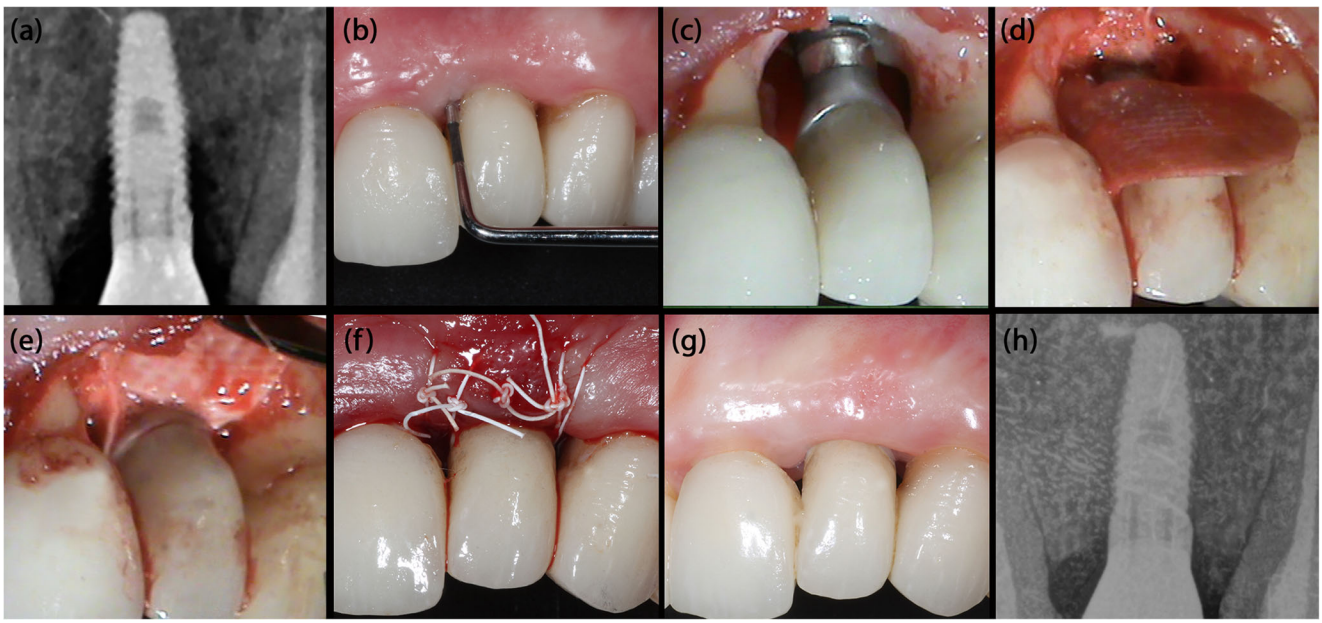

Fig. 1 **a** Baseline radiographic examination. **b** Clinical measurement at baseline (after non-surgical therapy). **c** Peri-implantitis defect configuration after complete granulation tissue debridement. **d** Vancomycin and tobramycin impregnated allograft is applied in the peri-implantitis defect. **e** Collagen membrane covering the entire defect. **f** The flap is repositioned allowing a non-submerged healing. **g** Clinical situation at 12-month follow-up. **h** Radiographic examination at 12-month follow-up

2nd week for the 1st month, and then, during the observation period of 1 year, patients were scheduled every 2 months. At each follow-up visit, a reinforcement of oral hygiene, supragingival debridement, and tooth polishing were performed. Twelve months after the surgery, a follow-up examination was performed (Fig. 1g, h).

Clinical measurements

The following clinical parameters were assessed for each implant by a single calibrated examiner (CV) at baseline and at the 12-month follow-up using a periodontal probe (PCP-UNC 15; Hu-Friedy, Chicago, IL, USA):

1. Plaque index (PlI): presence or absence of plaque along the mucosal margin [22]
2. Bleeding on probing (BoP): presence or absence of bleeding 15 s after gentle probing
3. Suppuration (SoP): presence or absence of suppuration after probing;
4. Peri-implant pocket depth (PPD): distance (mm) from the mucosal margin and the bottom of the probeable pocket
5. Mucosa recession (MR): distance (mm) from the mucosal margin and the implant abutment interface

Clinical examinations were performed at six sites per implant (i.e., mesiobuccal, buccal, distobuccal, distolingual, lingual, and mesiolingual) with the prosthetic reconstruction in place and rounded up to the nearest millimeter. The average was calculated to obtain the implant score (PPDm) and, additionally, the deepest PPD was used to represent the site (PPDd).

Radiological examination

A periapical radiograph was obtained using the long-cone parallel technique and a film holder (Dürr Dental AG, Bietigheim-Bissingen, Germany) at baseline, at 6- and 12-month follow-up visits. Care was taken to position the film parallel to the long axis of the implant. All radiographs were standardized in their exposure (7 mA-60 kV/20 ms).

The following measurements were recorded by an independent calibrated examiner (BdT) at the mesial and distal aspects of the treated implants:

1. Bone level (BL): distance (mm) between the implant shoulder and the bottom of the defect
2. Intrabony defect (ID): distance (mm) between the bottom of the defect and the line connecting the distal and mesial interproximal bone crest
3. Angulation of the intrabony defect (AD): angle between a vertical line along the outer implant surface and a line extending along the peri-implant bone defect

Average of mesial and distal aspect was calculated to obtain the implant score. Furthermore, the mesial or distal aspect corresponding to PPDd was used to represent the site.

The measurements were determined using an image-processing program (ImageJ; NIH, Bethesda, MA, USA). The radiographs were calibrated using the known dimensions of the implant as reference values.

Intra-examiner reproducibility

Reproducibility of radiographic and clinical examinations were conducted by the repeated examination of radiographic bone level and PPD record of 5 implants in 5 patients, 1 week apart, before the beginning of the study. The intra-examiner reliability was 0.87 for PPD and 0.98 for radiographic bone level (intraclass correlation coefficient).

Outcomes

Primary outcome measures included radiographic evidence of bone fill and changes in probing depths at implants treated.

Secondary outcome parameters were presence of plaque (% sites plaque), bleeding on probing (% sites BoP), suppuration on probing (% sites SoP), mean PPD, mean MR, mean radiographical BL, mean radiographical ID, and mean radiographical AD.

Statistical analysis

Shapiro-Wilk test was used to determine normality of the data and found to be non-Gaussian. For description of the data, mean values, standard deviations (SD), and frequencies were used. The six values of the clinical parameters PPD and MR recorded around each implant were averaged to obtain a mean implant score. In addition, the deepest PPD (PPDd) at baseline was used to represent the site. Regarding the radiological variables, BL, AL, and ID were recorded at mesial and distal sites around each implant and an average was calculated to obtain the implant score. Additionally, the BL, AL, and ID correspondent to the deepest PPD were used to represent the site. Percentages of bone fill were calculated regarding the initial infrabony defect. Mean changes between baseline and 1-year follow-up measurements were analyzed using the Wilcoxon signed-rank test. For categorical variables the pre-post evaluations were tested by McNemar test. The implant was the statistical unit of analysis. Statistical significance was set at the alpha level of 0.05. All statistical analysis was performed using a statistical software package (SPSS version 22.0; SPSS Inc., Chicago, IL, USA).

Results

A total of $n = 13$ consecutive patients (63.2% women and 26.8% men of 51–67 years old, mean 57.76 ± 6.21) with 17 infected implants completed the observation period of 12 months and served for the statistical analysis. In regard to tobacco use, 5 patients (38.5%) were light smokers (< 10 cigarettes per day) (Table 1).

In all cases the healing was considered as uneventful, no complications such as allergic reactions, swelling, or postoperative infection were observed throughout the entire follow-up period.

The distribution of the different implant systems and surfaces at baseline are reported in Table 2.

Clinical parameters of PlI, BoP, SoP, PPD, and MR measured at baseline and at 12 months are summarized in Table 3. Clinical examination at 12 months revealed peri-implant health, showing absence of suppuration in all patients and a statistically significant reduction of bleeding on probing score ($P = 0.001$). This was in concordance with the parameters of PPDd and PPDm, which were significantly reduced (4.23 ± 1.47 mm, $P = 0.001$ and 3.03 ± 1.21 mm, $P = 0.001$, respectively). However, a significant increase in mean MR (1.31 ± 0.47 mm, $P = 0.001$) was also reported following the regenerative surgery.

Radiographic data

The radiographic parameters at baseline and 12 months are presented in Table 4. At baseline, the mean BL was 4.99 ± 2.09 mm at the deepest site and 12 months after the surgery this value was reduced to 1.39 ± 1.45 ($P = 0.001$). Taking in consideration just the ID, the mean value at baseline was 4.33 ± 1.62 mm, and was significantly reduced up to 0.56 ± 0.88 mm. This reduction represented a 76.85 ± 28.27% of bone fill of the initial BL and 86.99 ± 18.2% of the initial ID; this difference was statistically significant ($P = 0.001$). When considering the average between the mesial and the distal aspect of each implant, a 76.94 ± 21.8% of bone fill of the initial BL and a 85.31 ± 24.39% of the initial ID was reached, leading to a residual ID of 0.46 ± 0.58 ($P = 0.001$).

Table 1 Demographic data

Number of patients	13
Number of implants	17
Gender	57.76 ± 6.21
Smoking	38.5% (5) light smokers/71.5% (8) never smokers
Type of suprastructure	58.8% (10) single crowns/41.2% (7) FDPs
Screw or cemented restoration	76.5% (13) screw-retained/23.5% (4) cemented
Location	58.8% (10) mandible/41.2% (7) maxilla
Years of function	8.2 ± 3.6

FDP fixed dental prosthesis

Table 2 Distribution of implant system at baseline

Distribution of implant system	TiUnite (Nobel Biocare®)	Shot blasting (Klockner®)	Biomimetic (Avinent®)	Laser-lok (Biohorizons®)
	6	4	5	2

Discussion

The present study showed that the treatment of peri-implantitis with a regenerative surgical approach by means of an antibiotic impregnated allograft yielded positive results in terms of PPD reduction and radiographic defect fill after 12 months.

Treatment of peri-implantitis remains to this day a controversial issue. There are many recommendations and alternative treatments, although there is no scientific evidence that demonstrates the superiority of one technique over another. The mechanical treatment demonstrated limited effectiveness, as well as the surgical resective treatment approach with low short-term success [23, 24]. Longitudinal studies have shown that peri-implant health at sites affected by peri-implantitis may not be easy to reestablish [25].

The efficacy of regenerative procedures in the treatment of peri-implatitis remains under discussion [26–28]. Clinical studies in humans demonstrated that PPD reduction as well as partial radiographic resolution of the defect could be achieved at sites treated with bone substitutes with or without a barrier membrane [29, 30]. However, authors concluded that complete fill of the bony defect using guided bone regeneration procedures is not predictable due to the existence of multiple factors that may be involved in the success of the treatment [31].

Table 3 Clinical parameters at baseline and at 12 months after treatment. Data are presented as mean ± SD and percentage

	Baseline	12 Months	*P* value
PlI (%)	18	25	0.577
BoP (%)	100	29.4	0.001*
SoP (%)	88.2	0	0.001*
PPDd(mm)	7.88 ± 1.22	3.66 ± 0.59	0.001*
PPDm(mm)	6.48 ± 1.26	3.45 ± 0.43	0.001*
MR (mm)	0.1 ± 0.31	1.42 ± 0.50	0.001*

PlI plaque index (O'Leary et al. 1972), *BoP* bleeding on probing, *SoP* suppuration on probing, *PPDd* probing pocket depth measured at the deepest site per implant, *PPDm* probing pocket depth when average of the 6 sites per implant was used, *MR* marginal recession

*Statistical significant differences ($P < 0.05$)

Table 4 Radiographic parameters at baseline and at 12 months after treatment. Data are presented as mean ± SD and percentage

	Baseline	12 Months	*P* value
Bone level measured at the deepest site (mm)	4.99 ± 2.09	1.39 ± 1.45	0.001*
Bone level measured as an average of mesial and distal aspects (mm)	4.29 ± 2.11	1.16 ± 1.34	0.001*
Intrabony defect measured at the deepest site (mm)	4.3 ± 1.62	0.56 ± 0.88	0.001*
Intrabony defect measured as an average of mesial and distal aspects (mm)	3.76 ± 1.32	0.46 ± 0.58	0.001*
Angulation of the deepest site (°)	32.04 ± 14.42	17.27 ± 24.91	–
Angulation average of mesial and distal aspects (°)	29.23 ± 16.34	14.52 ± 18.86	
Radiographic bone fill measured at the deepest site (mm)	–	3.75 ± 1.9 (86.99 ± 18.21%)	–
Radiographic bone fill measured as an average of mesial and distal aspects (mm)	–	3.30 ± 1.41 (85.31 ± 24.3%)	–

*Statistical significant differences ($P < 0.05$)

In a recent meta-analysis on the regenerative treatment of peri-implantitis, a pocket depth reduction of 3.16 mm (95% CI 2.54 to 3.78 mm) and a radiographic bone fill of 2.1 mm (95% CI 1.36 to 2.96 mm) was observed [32]. These results are in agreement with those reported by Sahrmann et al. [31] who observed that the regenerative therapy could achieve a mean PPD reduction of 3.29 mm, resulting in a residual pocket of 3.23 mm [31].

The mean pocket depth reduction obtained in the present case series was slightly superior, reaching 4.23 mm associated with an increased recession of 1.31 mm. Furthermore, the radiographic bone fill was 3.75 mm showing greater bone fill of about 1.5 mm compared to the mentioned literature.

In a prospective case series published by Matarasso et al., [33] reductions in PPD from 8.1 ± 1.8 to 4.0 ± 1.3 were obtained with an increased recession of 1.3 mm. These results are in accordance with the ones obtained in the present investigation. In this sense, surgical intervention methodology is very similar and differences between studies lie in type of graft used and antibiotic regimen (amoxicillin 875 mg and clavulanic acid 125 mg was prescribed twice daily for 5 days). This fact could point out that similar outcomes can be obtained by local delivery antibiotics avoiding oral administration.

In any case, efficacy of a treatment protocol for the resolution of the disease can be measured in different manners. Reestablishment of peri-implant health would ideally mean absence of clinical inflammation and bleeding on probing [34]. Furthermore, absence of bleeding can be considered as a reliable predictor for peri-implant stability [35]. A recent meta-analysis reveals a substantial change in BOP percentages after surgical regenerative interventions reaching a 50.2% of reduction [32]. In the present investigation, resolution of inflammation occurred in 70.6% of implants treated at 12 months follow-up. Prosthesis modification in order to facilitate oral hygiene at baseline may have contributed to this outcome.

It has been suggested that the outcome of the treatment of peri-implantitis can be also influenced by implant surface characteristics. Albouy et al. [9], in an experimental study in dogs, tested 16 implants with different surfaces, two of them were lost after surgical treatment showing a further bone loss at the 18-weeks reevaluation of 1.58 mm. In the present investigation although several implant surfaces with diverse degree of roughness were treated no differences were noted in the treatment outcomes, it could be speculated a broader scope in decontamination due to the local antibiotic delivery.

Due to heterogeneity in study designs, patient characteristics, materials utilized (i.e., the use or not of membranes and different types of bone grafts/bone substitutes), and evaluation methods, comparisons become difficult; however, from these data it could be speculated that, in the present investigation, the local delivery impregnated antibiotic helped to improve clinical and radiographic results. Decontamination of implant surfaces is difficult to achieve, since conventional treatment approaches, such as plastic curettes, sonic/ultrasonic scalers, and air-powder flow, have been proven to be insufficient for obtaining a complete removal and elimination of both plaque and biofilms [36]. This may be a logical reason for using locally delivered and/or systemic antibiotics as adjuncts to conventional peri-implantitis treatment protocols.

Local delivery antibiotics have been proven in some clinical studies in adjunction to mechanical non-surgical therapy to treat peri-implantitis lesions. Significant reductions in pocket probing depth and bleeding tendency after 12 months were found after combining mechanical therapy with the use of a tetracycline-containing fiber [37]. Along the same line, a controlled study demonstrated significantly greater gain in the mean attachment levels with the additional use of a slow-release doxycycline-containing preparation [10]. Furthermore, in a series of randomized-controlled studies, clinical benefits were reported after the adjunctive use of minocycline-containing microspheres [38–42].

The early healing in a low bacterial load environment has been reported to improve clinical outcomes in regenerative procedures [43]. Osteomycin V and T are characterized by having an antibiotic biofilm over the allograft particle, which is delivered over 2 weeks. About 60% of the biofilm is delivered after 2 days, 75% after 3 days, and more than 80% after 4 days. After 2 weeks, levels of about 5 μ g/ml are reached which becomes zero after an additional week [19]. The combination of locally delivered vancomycin and tobramycin might eliminate or reduce at a great extent the peri-implantitis biofilm [14, 19, 44] allowing for proper regenerative biological outcomes and even re-osseointegration. In addition, this antibiotic in a local concentration up to 1000 mg/l has demonstrated to have none or minimal effect on osteoblast replication [45].

To the superior clinical results obtained, we should also add the greater benefit of avoiding the use of systemic antibiotics and minimizing systemic toxicity. Local administration allows progressive delivery of active component directly to the target, achieving high and sustained concentrations that are difficult to obtain through the systemic route, besides, is independent of patient compliance [12]. Systemic antibiotics have secondary effects, which sometimes jeopardize/alter the regular life of patients. Moreover, today's antibiotic resistances arise an international health concern. Systemic antibiotics are taken often times without a scientific rational, and its abuse has driven the medical and dental community to possibly deliver them, when needed, locally [46].

To the best of our knowledge, this is the first clinical study evaluating the use of an antibiotic impregnated bone substitute for the regenerative treatment of peri-implantitis. It must be pointed out the methodological limitations present in the current case series study with respect to the study design and due to the absence of standardized clinical and radiographic examinations. Procedures and materials used in the current protocol need to be evaluated clinically in a broader sample, over a longer follow-up, and in randomized-controlled trials.

Nevertheless, and within the mentioned limitations, the findings from the present investigation suggest that sites treated with VTA and a cross-link collagen membrane result in clinical and radiographic improvements at 12 months of healing. Thus, these grafting materials might be suitable for the surgical regenerative treatment of peri-implantitis. The results obtained encourage to further investigate by means of randomized clinical trials in order to elucidate real benefits of this protocol.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants, were in accordance with ethical standards of the institutional research committee and with the principles stated in the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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