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Reconstruction of peri-implant osseous defects: A multicentre Randomized Trial

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	loss) as this finding was accomplished at 30% of implants in the test and 23% of implants in the control group. Reconstructive surgery using PTG resulted in significantly enhanced radiographic defect fill compared with OFD. Limitations in the lack of ability to discern biomaterial and osseous tissue could not be verified to determine new bone formation. Similar improvements according to clinical measures were obtained following both surgical treatment modalities.

Reconstruction of peri-implant osseous defects: A multicentre Randomized Trial

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Abstract

There is a paucity of data for the effectiveness of reconstructive procedures in the treatment of peri-implantitis. The objective of this study was to compare reconstruction of peri-implant osseous defects with porous titanium granules (OFD+PTG) with open flap debridement alone (OFD).

Sixtythree patients (36 female, 27 male; age: 58.4 ± 12.3 years), contributing one circumferential peri-implant intra-osseous defect were included in a multi-national, multicentre randomized trial using a parallel group design. Following open flap debridement and surface decontamination using titanium brushes and hydrogen peroxide, 33 defects received porous titanium granules. The implants were not submerged. All patients received adjunctive perioperative systemic antibiotics. The primary outcome variable defect fill was assessed on digitalized radiographs. Clinical measurements of probing depth (PPD), bleeding on probing (BoP), suppuration (PuS) and plaque were taken by blinded examiners.

After 12 months the test group (OFD+PTG) showed a mean radiographic defect fill (mesial/distal) of 3.6/3.6 mm compared to 1.1/1.0 in the control group (OFD). Differences were statistically significant in favour of the test group ($p < 0.0001$). The OFD+PTG group showed a mean reduction in PPD of 2.8 mm compared to 2.6 mm in the OFD group. BoP was reduced from 89.4% to 33.3% for the test and from 85.8% to 40.4% in the control group. There was no significant difference in complete resolution of peri-implantitis (PPD≤4 mm and no BOP at 6 implant sites and no further bone loss) as this finding was accomplished at 30% of implants in the test and 23% of implants in the control group.

Reconstructive surgery using PTG resulted in significantly enhanced radiographic defect fill compared with OFD. Limitations in the lack of ability to discern biomaterial and osseous tissue could not be verified to determine new bone formation. Similar improvements according to clinical measures were obtained following both surgical treatment modalities.

Trial registration NCT02406001

Key words: Debridement, peri-implantitis, surgical therapy, titanium granules, bone regeneration, dental/oral implants

Introduction

Peri-implant osseous defects are often the result of peri-implantitis defined as inflammation of peri-implant tissues accompanied by peri-implant bone loss with bleeding on probing and/or suppuration, with or without concomitant deepening of peri-implant pockets (Lang and Berglundh 2011). According to recent reviews, this infectious condition has a prevalence of 20% of patients (Mombelli et al. 2012; Klinge and Meyle 2012; Atieh et al. 2013; Derks and Tomasi 2015).

Various protocols including mechanical debridement, the use of antiseptics and local or systemic antibiotics, as well as access and regenerative surgery have been proposed for the treatment of peri-implantitis. At present there is no reliable evidence to identify the most effective intervention for treating peri-implantitis (Esposito et al. 2012).

Surgical methods are commonly applied for the management of moderate and advanced peri-implantitis (Aljateeli et al. 2012). One of the goals of surgical therapy is access for implant surface decontamination. An anti-infective protocol, incorporating surgical access, surface decontamination and systemic antimicrobials was shown to be effective in a 12-months follow-up (Heitz-Mayfield et al. 2011). Regenerative procedures, using bone grafts or bone substitutes, sometimes in combination with membranes, aimed at reconstructing peri-implant osseous defects have shown variable results (Khoury and Buchmann 2001; Roos-Jansaker et al. 2007a/b, 2011, 2014; Schwarz et al. 2009; 2010, Aghazedeh et al. 2012; Wiltfang et al. 2012). However, there is only limited evidence in the literature available to compare the clinical effectiveness of reconstructive and nonreconstructive procedures (Khoshkam et al. 2013).

Recently porous titanium granules (PTG) have been introduced as an osteoconductive bone graft substitute for the treatment of peri-implant defects. A case report with human histology demonstrated that grafting of a peri-implant defect with PTG could support re-osseointegration of the implant with newly formed bone (Wohlfahrt et al. 2011). In a randomized controlled trial Wohlfahrt et al. (2012) compared open flap debridement (control) with a surgical procedure placing PTG (test) for augmentation of peri-implant osseous defects in a submerged surgical

technique and found significantly better radiographic peri-implant defect fill compared with the controls. In a case report the reconstruction of a peri-implant defect with PTG was preceded by implant surface debridement with a novel titanium brush and H_2O_2 (3%). Re-entry surgery after 6 months revealed a complete integration of the bone replacement material in new bone, with no signs of loose particles (Wohlfahrt & Lyngstadaas 2012).

The objective of the present randomized trial was to compare reconstructive surgery of advanced peri-implant osseous defects with PTG to open flap debridement in a non-submerged technique, with the hypothesis of a significantly higher defect fill after 12 months for the reconstructive procedure.

Material and Methods

Study design

The study was designed as a prospective multicentre, multi-national, randomized, parallel-group clinical trial of 12 months duration and registered at ClinicalTrials.gov (NCT02406001).

All investigators attended calibration meetings where preliminary cases were discussed and used to standardize case selection, clinical measurement techniques and surgical procedures.

On-site rules for the compilation of the data collection sheets for appropriate oversight were frequently reassured by a study monitor to ensure the validity of the data.

Study population

Study subjects were recruited consecutively from patients treated by experienced periodontists/implant dentists in Germany (University of Bonn), the Netherlands (Amsterdam, ACTA), Italy (Rome University), Spain (University Complutense Madrid) and Sweden (Kristianstad University). After thorough explanation of the study procedure and its associated risks and benefits each participant signed an informed consent in accordance with the Helsinki Declaration of 1975 as revised in 2008. The Ethical Committee for human subject trials in each institution approved the study protocol individually.

Seventy informed and consenting patients above the age of 18 years of age with a diagnosis of peri-implantitis were enrolled in the study and surgery was performed. Seven patients were withdrawn early at surgery, as the defect around the implants did not meet the inclusion criteria. After surgery 63 patients (36 female and 27 male; mean age: 58.4 ± 12.3 (SD) years; range: 26 to 88 years) remained in the study (Test group n = 33, Control group n = 30). A study flow chart is presented as Figure 1.

Inclusion criteria

All implants had to be in function for more than 12 months. In patients with more than one peri-implant defect meeting the inclusion criteria only one implant per patient was defined as target (the most severe defect) and included in the study.

Primary inclusion criteria

By initial radiographic evaluation:

- Intraosseous defect ≥ 3 mm on standard intraoral radiograph.

By clinical evaluation:

- Peri-implant probing depth (PD) ≥ 5 mm
- Bleeding (BOP) and/or suppuration (PUS)

Secondary inclusion criteria

By intra-operative exploration:

- Intra-osseous defect component ≥ 3 mm at the deepest point
- 3 to 4 walls
- Defect with at least 270 degrees (circumferential)
- Defect angle ≤ 35 degrees (from axis of implant)

Exclusion criteria

- Subjects with diabetes mellitus (HbA1c ≥6.5).
- Subjects taking corticosteroids or other anti-inflammatory prescription drugs.
- Subjects taking medications known to induce gingival hyperplasia.
- Subjects with a history of taking systemic antibiotics in the preceding month.
- Patients pregnant or nursing.
- Implants placed in grafted bone or previously augmented with bone /bone substitute.
- Implants previously surgically treated for peri-implantitis.
- Implant mobile.

Pre-surgical treatment and evaluation

All necessary periodontal treatments were finished as evaluated by a full periodontal examination with recording of pocket probing depth (PPD), full-mouth bleeding and plaque scores at least 1 month prior to the peri-implant surgical procedure and to entry into the study. Pre-surgical interventions included oral hygiene instructions to the individual needs of the patient, non-surgical periodontal/periimplant and surgical periodontal therapy.

Patients who met all criteria for inclusion, verified at surgery, underwent investigational procedures. Baseline measurements at the included implant were performed on the same day as the surgical procedure.

Radiographic measurements

Intra-oral peri-apical radiographs were obtained of implants in a standardized way using Eggen holders and long cone equipped dental X-ray units. All radiographs presenting study implants were digitalized, coded and evaluated by a computer program (MATLAB® Vers. R2013b software for MAC OS 10.9; Mathworks, Natick, MA, USA).

Radiographs were studied by changing parameters in black and white modus as well as in colour look-up tables. Measurements from a well-defined reference point at the coronal part of the implant body taken at baseline 6 and 12-months visits were: vertical defect depth and width, marginal bone level and horizontal bone level (Figure 2, supplementary Figure 3). Based on these measurements, changes in vertical defect depth, marginal bone level, % defect fill and % defect resolution from baseline to 12 months were calculated.

The most coronal confluent aggregation of bone or bone with graft material was used to define marginal and horizontal bone levels. Titanium particles without visible mineralized tissue adjacent to the implant did not count as most coronal bone-to-implant contact. Likewise single isles of bone or bone-like material were not considered.

Implant length and width or known dimensions of implant-threads were used as reference for calibration of measurements. Radiographic evaluations were initially performed by an independent physicist (PNJ), with high expertise in image analysis, who was not involved in other aspects of the study. He had previously been

extensively trained by a periodontist experienced in oral radiology on sample images on a LCD-display with a resolution of 2560 x 1600 and a 32-Bit colour pixel depth. All measurements performed were saved as graphics placed on top of the corresponding image and were then independently confirmed by two periodontists. No double measurements of radiographs were performed. If differences were > 0.1 mm, the three calibrated investigators re-analysed the respective implant together to reach a consensus (Enkling et al. 2011a,b, 2013).

Clinical measurements

For proper standardization between baseline and re-evaluation data, only one examiner took all the clinical measurements in each study centre. All probing measurements were obtained with a pressure (0.20-0.25N) sensitive probe (Click-Probe®, Kerr, Switzerland) to the nearest mm at 6 sites per implant (mesio-buccal, buccal, disto-buccal, disto-palatal, palatal, mesio-palatal).

At baseline and 12 months visits, the following recordings were taken:

- Probing pocket depths (PPD)
- Bleeding on probing (BoP)
- Suppuration (PUS)
- Plaque

BoP and PUS at the affected implants were assessed within 30 seconds following probing.

At surgery intraoperative measurements included:

- Defect depth (mm) at the deepest point
- Defect circumference (degrees),
- Defect walls (number)
- Defect width (mm)

Sample size calculation/Power Analysis

The calculation of the number of patients to be treated (sample size) was based on a previous proof-of-concept single-centre RCT (Wohlfahrt et al. 2012) and the primary

objective to detect a true mean difference of at least 2 mm between test and control treatment for radiographic defect fill after 12 months. With a level of significance of alpha = 0.05 in a two-sided hypothesis and a power of 90 %, the number of patients needed was 48. Assuming a dropout rate of about 30% the total number of patients required was 60.

Randomization, Allocation concealment and Blinding

Patients were randomly assigned to treatment modality by using a computerized randomization scheme prepared prior to study initiation and to treatment in blocks of 6. The patients were allocated to either reconstruction of the defect with PTG (Test) or closure of the flap after implant debridement (OFD/Control). Documentation of treatment allocation for each patient was placed in separate, sealed opaque envelopes that were opened and revealed to the surgeon after debridement of the defect and implant surface was finished. Clinical examiners and the statistician remained blinded to the treatment assigned.

Interventions

Surgical Procedure

A non-submerged surgical technique was used for both test and control sites. Following administration of local anaesthesia flap elevation procedure included an intra-crevicular incision around the implant. Full thickness mucoperiosteal flaps were raised on the buccal and lingual aspect to gain access to the complete peri-implant defect and to the implant surface. The size of the flap was determined by supra-crestal incisions extending mesial and distal of the implant site. Vertical incisions into the vestibule at a distance of at least one tooth/implant from the implant were performed as necessary for adequate access. Granulation tissue was removed using titanium curettes (HuFriedy®, Chicago, IL, USA) and the exposed implant surfaces were cleaned mechanically by using a rotary titanium brush (Tigran PeriBrush™, Tigran Technologies, Malmö, Sweden) and decontaminated chemically with 3% H_2O_2 for 1 minute followed by rinsing with saline for 60 seconds (2 x 20 ml).

Following treatment allocation in accordance to randomization, titanium granules (Tigran™, Tigran Technologies, Malmö, Sweden) were applied into the intraosseous defects of the test sites. After insertion of the granules, excess material was carefully removed. Flaps were then repositioned and sutured back into position using

monofilament non-resorbable sutures.

Peri-operative protocol

Patients were prescribed a combination of Amoxicillin 500 mg 3/day and Metronidazole 400 mg 2/day for 8 days, starting one day prior to surgery. Patients were then instructed to rinse twice daily with chlorhexidine mouth rinse (0.2%) for 1 month. The patients used brushes as usual in other areas of the mouth. Anti-inflammatory and analgesic therapy was prescribed (Ibuprofen 3 x 600 mg/day) during the first two days and according to the individual needs thereafter.

The sutures were removed after 7 to 14 days and patients were instructed in the use of soft toothbrushes and soft interdental brushes (super soft – Gentle/Implant Care TePe, Malmö, Sweden) in the surgical area.

Patients were recalled at 6 weeks, 3, 6, 9 and 12 months after surgery for professional oral hygiene procedures with supra-gingival debridement and hygiene instructions as needed.

Pre-defined early withdrawal criteria were:

- non healing infections
- substantial exfoliation of graft material (rejection)
- local intolerance to graft material
- recurrence of active peri-implantitis at the test site
- loosening of implant
- poor patient compliance, not returning for control visits

Statistical Analysis

Primary outcome was defect fill as assessed by changes of radiographic marginal bone level and vertical defect depth.

Secondary outcomes were changes in:

- PPD
- BoP
- Suppuration/Pus
- Plaque

Analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). All patients included in the study had surgery performed and were analyzed for side effects. Four patients were excluded from analysis because there were no data available at 12 months (Figure 1).

Statistical analysis of primary efficacy endpoint measures was performed using centre as stratification variable. As a significant interaction between baseline measurements and treatment was observed for vertical defect depth measures a stratified Wilcoxon test (Lehmann 1975, van Elteren 1960) was applied.

Treatment intergroup comparisons of secondary efficacy endpoints were based on least squares means obtained from the ANCOVA model. Means for each treatment group and differences between treatment groups are presented along with associated 95% Confidence Intervals (CI) as well as p-values for differences within treatment groups.

The statistical hypotheses for the **Primary Outcome** *defect fill (mm)* was:

H0: Δ Marginal bone level $_{Test}$ – Δ Marginal bone level $_{control}$ = 0

H1: Δ Marginal bone level $_{Test}$ – Δ Marginal bone level $_{control}$ ≠ 0

and :

H0: Δ Vertical defect $_{Test}$ – Δ Vertical defect $_{control}$ = 0

H1: Δ Vertical defect $_{Test}$ – Δ Vertical defect $_{control}$ ≠ 0

For percent changes the statistical hypotheses were based on:

$$\%\,Defect\ resolution = (Vertical\ defect_{baseline} - Vertical\ defect_{12months})/(Vertical\ defect_{baseline}) \times 100$$

$$\%\ Defect\ Fill = (Marginal\ bone\ level_{baseline} - Marginal\ bone\ level_{12months})/(Vertical\ defect_{baseline}) \times 100$$

If the p-value from this analysis fell below 0.05 in both mesial and distal measurements it was concluded that there was a statistically significant difference in average change between the two treatment groups.

Results

Between February 2010 and December 2013 a total of 105 patients were consecutively recruited at the 5 study centres (16 – 36 per centre). Seventy patients fulfilled the primary and 63 the secondary inclusion criteria and were randomized to test (n = 33) and control (n = 30) group. Four patients of the control group refused to participate at the 12 months recall appointment and were lost to follow-up. The number of participants per centre ranged from 10 to 13. Baseline characteristics and demographics for subjects in the two study groups are presented in Table 1.

Radiographic and clinical findings are presented in Table 2 and effects of treatment as changes in radiographic and clinical parameters are presented in Table 3. Significantly higher reductions of vertical defect depth and gains in marginal bone level favoured the PTG reconstructed group (<0.0001). After 12 months the mean gain of marginal bone level for the Test group was 3.61/3.56 mm (mesial/distal) compared to 1.05/1.04 mm (mesial/distal) in the OFD group. This corresponded to a mean defect fill for the PTG treated sites of 79.00/74.22% (mesial/distal) compared with 23.11%/21.89% (mesial/distal).

No differences in defect width and horizontal bone level changes could be observed (supplementary table 4).

The test group showed a mean reduction in PPD of 2.8 mm (SD 1.3) compared to 2.6 mm (SD 1.4) in the OFD group. Reductions for BoP amounted to 56.1% for the test compared to 44.9% for control group. Intergroup differences for PPD or BoP reduction were not found to be significantly different.

In both treatment groups 30% of implants showed disease resolution by absence of any bleeding on probing, whereas 30% (test) and 23% (control) of implants demonstrated successful peri-implantitis therapy by the use of a composite outcome that also included shallow pockets and no further bone loss (Table 2).

None of the patients treated demonstrated subjective or objective side effects, such as pronounced pain, manifest inflammatory reactions, discoloration of the surrounding mucosa, or patient morbidity, beyond what is normally expected for similar surgical procedures.

Discussion

The present randomized multi-national, multicentre trial demonstrated additional benefits following reconstructive surgery with application of porous titanium granules in combination with an open flap non-submerged debridement procedure for the treatment of advanced peri-implant osseous defects when compared to open flap debridement alone. Mean radiographic defect fill, as the primary outcome, amounted to 3.6 mm translating into a mean defect fill of about 79%, which was significantly higher than 1.0 mm (22%) observed in the control group. Thus, the study null-hypothesis assuming no difference in defect fill could be rejected.

With regard to secondary outcome measures, there were no statistically significant differences in reduction of pocket depths and bleeding on probing. Both surgical treatment modalities resulted in marked improvements of the clinical conditions.

To the best of our knowledge, this is the largest published randomized trial to evaluate the effectiveness of reconstructive peri-implant surgery and one of the very few that used open flap debridement for comparison, as demanded by a recent systematic review (Koshkam et al. 2013). It adopted the current guidelines for quality of methods and reporting for studies of the efficacy of therapeutic approaches to peri-implant diseases (Graziani et al. 2012) from a recent consensus conference, where multi-center approaches were encouraged (Sanz and Chapple 2012). The fact that different surgeons in a variety of settings treated a wide range of implants types enhances the generalizability of the obtained results.

There are also some limitations inherent in any study of the present design. First, a radiographic examiner cannot be blinded due to the use of a radiopaque bone substitute. We tried to compensate for this shortcoming by employing 3 independent calibrated examiners. Second, the amount of bone fill has to be interpreted with caution, whenever radiopaque bone substitutes are used. In this regard the choice of a distinctly visible material such as titanium granules may have advantages compared to other non/slow-resorbable bone substitutes (such as for example natural bone mineral/deproteinized bone xenograft), as it can be more clearly distinguished from the surrounding bone. The possibility of pure “x-ray-cosmetics” becomes less likely. Third, it has to be realized that re-osseointegration/regeneration cannot be evaluated by a clinical study. Regarding the healing of PTG applied to

peri-implant osseous defects, 2 case reports, one using human histology and another a re-entry procedure, can help to interpret the radiographic findings of the present study. Human histology demonstrated that grafting of a peri-implant defect with PTG could support re-osseointegration of the implant with newly formed bone (Wohlfahrt et al. 2011), and re-entry surgery of a treated peri-implant defect after 6 months revealed a complete integration of the bone replacement material in new bone, with no signs of loose particles (Wohlfahrt and Lyngstadaas 2012). Further evidence comes from recently published clinical studies on the use of PTG for sinus augmentation, where biopsies employing histological and micro-CT analyses confirmed osteoconductive properties of porous titanium granules (Dursun et al. 2015, Lyngstadaas et al. 2015, Verket et al. 2013, Vandeweghe et al. 2013).

Another possible shortcoming in the present study was the fact that the inter-examiner agreement for the clinical parameters could not be assessed due to logistical and financial constraints. All clinical examiners were very experienced, had shown good intra-examiner reproducibility in the past and measures were taken to standardize the probing assessment as much as possible. In particular, the use of a pressure sensitive probe was considered to be very important for the reliable and reproducible assessment of peri-implant bleeding (Lang et al. 2000). Any bias resulting from a possible low inter-examiner reproducibility would have affected to a similar extent both the test and the control group and therefore most likely not the outcome of the efficacy analysis of this RCT.

Another possible confounder could be the distribution of different implant types in the test and control group. Even though at present there are no data from clinical studies on the influence of implant microstructure and other surface characteristics on the response to reconstructive treatment the possible impact of such implant features on the outcomes can not be ruled out.

All four of the dropout patients were from the control group. This could also have an impact on the results. We have checked the baseline characteristics of the drop-outs and were able to confirm that they were not outliers in any aspect.

The results of the present study compare favourably with the weighted means of 2.17 mm (95% CI: 1.46-2.87 mm), 2.1 mm (95% CI: 1.47-2.72 mm), and 2.16 mm (95% CI: 1.36-2.96 mm), respectively, for radiographic defect fill reported in recent

systematic reviews on the outcomes of reconstructive/regenerative procedures in the treatment of peri-implantitis (Khoshkam et al. 2013; Chan et al. 2014).

Comparing the results of the present multicentre RCT with the previous single-center RCT on the use of PTG (Wohlfahrt et al. 2012) similar differences were seen. In their study, using a submerged design for the healing phase, radiographic peri-implant defect fill was significantly increased with application of PTG (2.0 +/- 1.7 mm) compared with non-grafted control group (0.1 mm +/- 1.9 mm). Event though both studies used systemic antibiotics, differences in flap design, and in particular characteristics of the peri-implant osseous defects treated might be responsible the difference in the magnitude of the outcomes (Schwarz et al. 2010). Another contributing factor could be the implant decontamination procedure. Wohlfahrt et al. (2012) used titanium curettes and 24% EDTA, whereas in the present study a titanium brush in combination with 3% H_2O_2 was employed. When comparing control groups of the two studies, differences in radiographic defect fill are obvious, as our control group showed an average defect reduction of 1 mm after 12 months. In contrast, in the earlier investigation the non-grafted control group did not improve at all after treatment (0.1mm +/- 1.9mm). In the present study anti-infective OFD using a titanium brush with H_2O_2 decontamination of the implant surface even led to complete radiographic bone fill up to the implant shoulder in one implant.

Finally, a retrospective cohort study using PTG for peri-implantitis lesions in 18 implants in 16 patients reported a reduction of mean bone loss from 4.4 to 2.3 mm (Mijiritsky et al. 2013).

With regard to secondary outcomes, the present study showed marked clinical improvements by reduction in inflammation (BoP and suppuration) and reduction in mean PPD in both treatment groups. Mean BoP reductions of 56% in the test group compare favourably with the weighted mean of 45.8% in a recent systematic review (Koshkam et al. 2013). The proportion of implants with absence of any bleeding at 6 sites amounted to 30% in both groups. Likewise, mean PPD reductions of 2.8 mm in the test group are in concert with the weighted mean of 2.9 mm in a recent meta-analysis (Koshkam et al. 2013). PPD reductions in the control group are in agreement with a recent meta-analysis of studies using access flap and debridement (Chan et al. 2014). In the interpretation of these findings a significantly improved full mouth plaques score in the control group, which was not seen in the test group,

should be kept in mind.

The use of composite therapeutic endpoints for the surgical management of peri-implantitis has been recently recommended (Sanz and Chapple 2012) and they were applied in the present study. Disease resolution by presence of shallow pockets without any bleeding at 6 sites of the implants and no further bone loss could be demonstrated for 30% of implants in the test and 23% of implants in the control group. While such an endpoint would be the ideal goal of peri-implantitis therapy and measure for success no other studies have reported such composite outcomes (Heitz-Mayfield and Mombelli 2014).

In the present study, no barrier membrane was used to cover the bone substitute. For the contained defects this additional measure which would add more costs was not felt to be necessary, even though a recent meta-analysis demonstrated higher PD and BOP reduction following grafts and barrier membranes than following grafts alone (Chan et al. 2014). A long-term follow up study showed a significantly better outcome following natural bone mineral in combination with a collagen membrane compared to a resorbable hydroxyapatite after 4 years (Schwarz et al. 2009). In contrast, Roos-Jansaker et al. (2015) found no additional effect from the application of a barrier membrane to a bone graft. Future studies will have to show whether membranes or the use of a non/slow-resorbable bone substitute are of key importance to ensure long-term stability of the results of reconstructive peri-implant surgery.

Within the limitations of the present study, it can be concluded that surgical treatment approaches which included the use of a titanium brush for implant surface dcontamination and adjunctive systemic antibiotics have shown promising results for the treatment of advanced peri-implant osseous defects. No significant differences were observed regarding the clinical outcomes bleeding and pocket reduction as well as for complete resolution of peri-implantitis between test and control procedures. The radiographic findings have to be interpreted with caution, as it is difficult to discern biomaterial and newly formed osseous tissue. Therefore, the relevance and potential benefit of an enhanced radiographic defect fill following application of porous titanium granules into 3- and 4-wall defects will have to be evaluated by further histological studies and a long-term clinical follow up.

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Figure legends

Figure 1: CONSORT flow chart.

Figure 2: Radiographic measurements at baseline and after 12 months.

Supplementary Figure 3: Radiographs showing peri-implant osseous defects before and after treatment for Test (a, b, c) and Control group (d, e, f).

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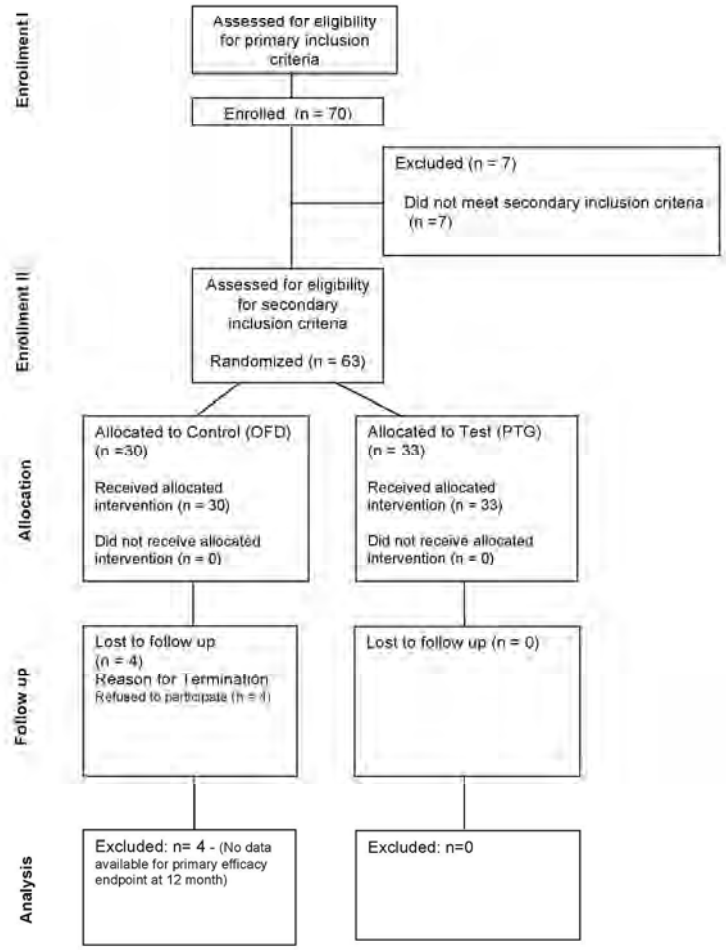

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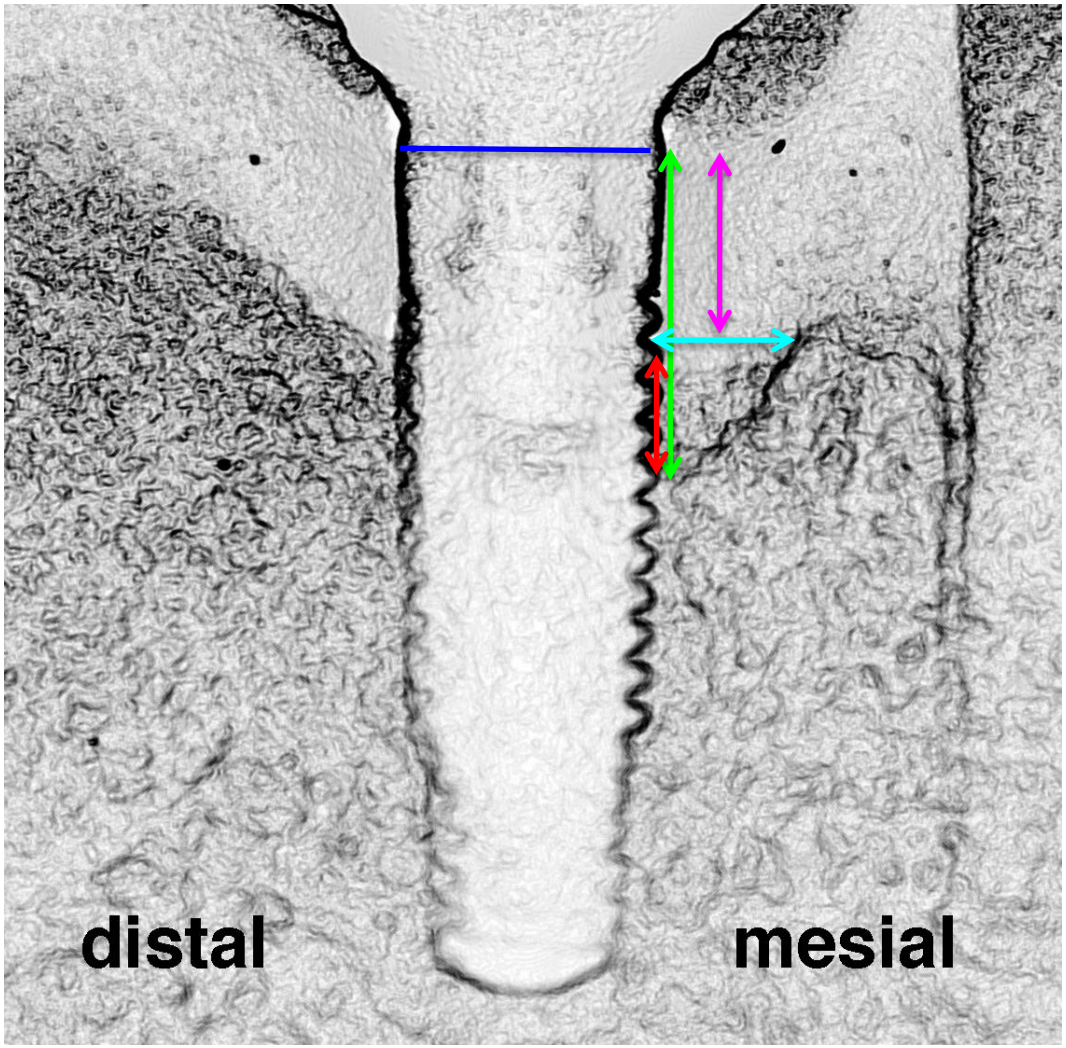


A Vertical Defect Depth
B Defect Width
C Marginal bone level
D Horizontal bone level
E Implant shoulder

Table 1 : Patient Characteristics at Baseline.

	Test (PTG) (n=33)	Control (OFD) (n=30)
Age (years), mean (SD)	57.7 (12.6)	59.1 (12.2)
Male (n)	16 (48.5%)	11 (36.7%)
Female (n)	17 (51.5%)	19 (63.3%)
Reason for placing implants		
Caries	10 (30.3%)	9 (30.0%)
Other	6 (18.2%)	2 (6.7%)
Periodontitis	11 (33.3%)	16 (53.3%)
Trauma	6 (18.2%)	3 (10.0%)
History of Periodontal Treatment		
No	13 (39.4%)	10 (33.3%)
Unknown	3 (9.1%)	0 (0%)
Yes	17 (51.5%)	20 (66.7%)
Smoking status		
Current	11 (33.3%)	7 (23.3%)
Former	9 (27.3%)	11 (36.7%)
Non-smoker	13 (39.4%)	12 (40.0%)
Implant Brands		
Ankylos	2	1
Astra (OsseoSpeed)	6	4
Dyna	1	
Friadent Xive	1	2
Nobel Biocare	10	8
SIC Invent		1
Straumann (Standard neck)	5	5
TRI MAX		1
TMI	3	2
Zimmer	4	2
3i Biomet	1	4

Table 2: Radiographic and Clinical Parameters at Baseline and 12 Months.

		Test (OFD+PTG) n = 33			Control (OFD) n = 26		
		BL	12M	P-value	BL	12M	P-value
Vertical defect depth (mm) Mean (SD)	*mesial*	4.64 (1.95)	1.03 (1.35)	<0.0001	3.98 (2.50)	2.88 (1.86)	NS
	distal	4.63 (2.26)	1.06 (1.51)	<0.0001	3.79 (1.75)	2.72 (1.77)	NS
Marginal Bone level (mm) Mean (SD)	*mesial*	5.55 (2.30)	1.98 (1.99)	<0.0001	4.63 (2.68)	3.63 (2.34)	0.0001
	distal	5.41 (2.72)	1.96 (1.95)	<0.0001	4.45 (2.23)	3.63 (2.32)	0.0007
Defect width (mm) Mean (SD)	*mesial*	2.53 (1.25)	1.33 (1.78)	<0.0001	2.28 (0.89)	2.11 (1.07)	NS
	distal	2.65 (1.57)	1.55 (1.88)	<0.0001	2.34 (1.11)	1.92 (1.41)	NS
Horizontal bone level (mm) Mean (SD)	*mesial*	0.91 (1.31)	0.95 (1.44)	NS	0.64 (1.06)	1.30 (3.24)	NS
	distal	0.78 (1.40)	0.92 (1.27)	NS	0.66 (1.33)	0.90 (1.35)	NS
PPD (mm) Mean (SD)		6.3 (1.3)	3.5 (1.5)	<0.0001	6.3 (1.6)	3.5 (1.1)	<0.0001
	mesial	6.9 (2.0)	3.7 (1.8)	<0.0001	6.3 (1.8)	3.9 (1.3)	<0.0001
	distal	6.5 (1.3)	3.6 (1.5)	<0.0001	6.6 (1.6)	3.6 (1.2)	<0.0001
BoP (%)* Mean (SD)		89.4 (20.7)	33.3 (31.7)	<0.0001	85.8 (23.9)	40.4 (37.1)	<0.0001
PUS (%)** Mean (SD)		27.8 (34.0)	1.0 (4.2)	<0.0001	25.9 (33.1)	1.3 (4.6)	<0.0001
PI (%)** Mean (SD)		25.8 (36.8)	24.8 (36.3)	NS	21.0 (28.7)	10.3 (20.0)	0.02
Implants (%) **with:**							
Absence of BoP ***		0	10 (30.3)		0	8 (30.8)	
PPD ≤4 mm* and **Absence of BoP*** and **no further bone loss**		0	10 (30.3)		0	6 (23.0)	

*BoP Bleeding Score Index out of 6 sites per implant.
** PUS | Plaque Score out of 6 sites per implant
*** at 6 implant sites

Table 3: Change in Radiographic and Clinical Parameters between Baseline and 12 Months.

Mean (SD)		Test (OFD+PTG)	Control (OFD)	Test vs. Control p-value
Vertical defect depth (mm)	*mesial*	-3.61 (1.96)	-1.05 (1.42)	<0.0001
min:max		-9.4 : -0.3	-5.7 : 1.9	
	distal	-3.56 (2.07)	-1.04 (1.34)	<0.0001
min:max		-9.0 : 0.3	-3.9 : 1.6	
Marginal bone level (mm)	*mesial*	-3.58 (2.05)	-0.96 (1.35)	<0.0001
min:max		-9.9 : 0.3	-4.7 : 1.9	
Estimate (95% CI)		-3.41 (-3.94 : -2.89)	-1.21 (-1.81 : -0.62)	
	distal	-3.45 (2.16)	-0.84 (1.14)	<0.0001
min:max		-9.0 : 0.3	-3.9 : 1.0	
Estimate (95% CI)		-3.28 (-3.81 : -2.75)	-1.11 (-1.72 : -0.50)	
Defect resolution (%)*	*mesial*	78.83 (27.25)	24.10 (40.01)	<0.0001
	distal	77.95 (28.82)	25.79 (36.02)	<0.0001
Defect fill (%) **	*mesial*	79.00 (29.85)	23.11 (46.28)	<0.0001
	distal	74.22 (36.33)	21.89 (30.16)	<0.0001
PPD		-2.8 (1.3)	-2.6 (1.4)	NS
Estimate (95% CI)		-2.81 (-3.17: -2.46)	-2.66 (-3.06 : -2.25)	
	mesial	-3.2 (1.9)	-2.2 (1.6)	NS
Estimate (95% CI)		-3.02 (-3.47 : -2.56)	-2.47 (-2.99 : -1.96)	
	distal	-2.9 (1.5)	-2.9 (1.6)	NS
Estimate (95% CI)		-3.02 (-3.47 : -2.56)	-2.71 (-3.14 : -2.29)	
BoP (%)***		56.1 (30.5)	44.9 (38.2)	NS
Estimate (95% CI)		-55.34 (-65.44 : -45.24)	-45.52 (-56.97 : -34.07)	
PUS (%)****		-23.2 (32.8)	-25.6 (32.7)	NS
Estimate (95% CI)		-22.79 (-27.69 : -24.59)	-25.99 (-31.53 : -20.45)	
PI (%)*****		-1.0 (37.5)	-11.5 (34.2)	NS
Estimate (95% CI)		-0.43 (-10.50 : -9.74)	-12.91 (-24.39 : -1.44)	

*defined as: (Vertical defect $_{baseline}$- Vertical defect $_{12months}$)/(Vertical defect $_{baseline}$) x100
** defined as: (Marginal bone level $_{baseline}$- Marginal bone level $_{12months}$)/(Vertical defect $_{baseline}$) x100
***BoP Bleeding score index out of 6 sites per implant.
**** PuS Score out of 6 sites per implant.
***** Plaque Score out of 6 sites per implant.

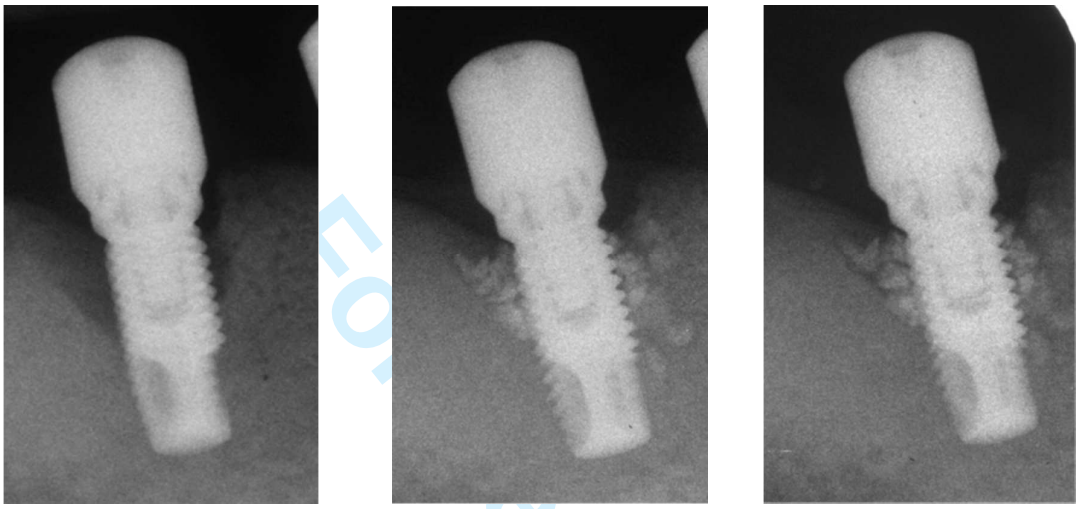
Supplementary Table 4: Changes in Radiographic Defect Width and Horizontal Bone Level between Baseline and 12 Months.

Means (SD)		**Test (OFD+PTG)**	**Control (OFD)**	**Test vs. Control** p-value
Defect width (mm)				
Estimate (95% CI)	*mesial*	1.20 (1.58) -1.16 (-1.59 : -0.73)	0.12 (0.77) -0.21 (-0.70 : 0.28)	NS
Estimate (95% CI)	*distal*	1.10 (1.65) -1.06 (-1.57 : -0.55)	0.35 (1.39) -0.47 (-1.06 : 0.13)	NS
Horizontal bone level (mm)				
Estimate (95% CI)	*mesial*	0.04 (0.97) -0.01 (-0.77 : 0.76)	0.63 (3.09) -0.63 (-0.23 : 1.50)	NS
Estimate (95% CI)	*distal*	0.15 (1.07) 0.16 (-0.15 : 0.46)	0.19 (0.75) 0.18 (-0.17 : 0.54)	NS

Supplementary Figure 3: Radiographs showing peri-implant osseous defects before and after treatment for Test (a, b, c) and Control group (d, e, f).

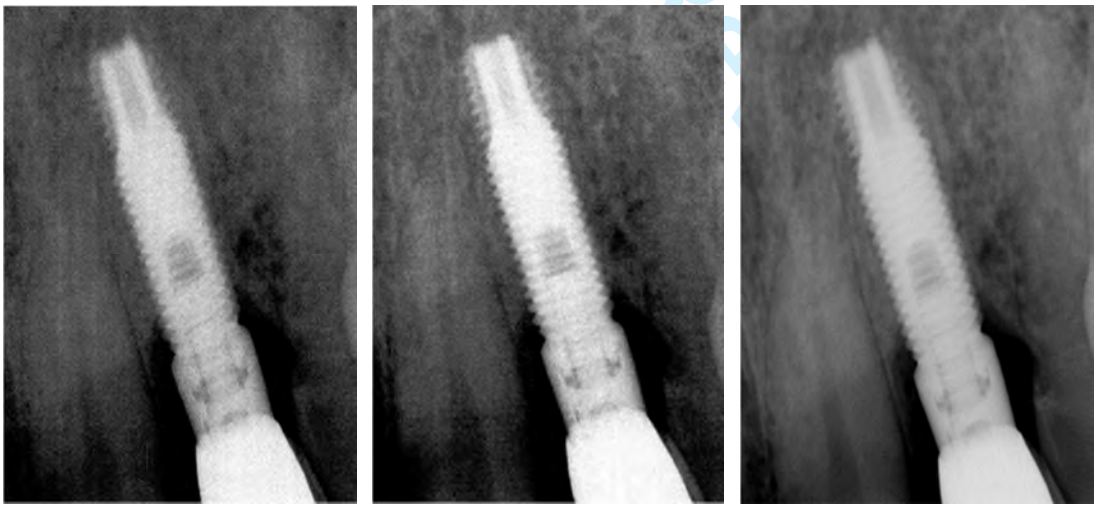
Test group:

a) Baseline b) 6 Months c) 12 Months



Control group:

d) Baseline e) 6 Months f) 12 Months



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3, 4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9, 10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8, 10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	8, 9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1,2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3 Sup. Table 4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2, 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12,13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14,15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14, 15, 16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15, 16, 17
Other information			
Registration	23	Registration number and name of trial registry	ClinicalTrials NCT02406001
Protocol	24	Where the full trial protocol can be accessed, if available	ClinicalTrials
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Tigran Technologies