Italian Society
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Henry M. Goldman Prize 2015

Membranes and bone substitutes in a one-stage procedure for horizontal bone augmentation. A double-blind randomised clinical trial

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SIdP – Proceedings Book H.M. Goldman - Rimini, 6 March 2015

SUMMARY

Aim: The objective of this RCT was to compare two bone materials and collagen membranes in a one-stage procedure for horizontal bone augmentation: Bio-Oss® and Bio-Gide® (BB) versus Ceros-TCP® and Jason® (CJ).

Methods: Patients were randomised to receive either BB or CJ.

Results: Twenty-five patients with 32 implants were allocated to the BB group and 25 patients with 29 implants to the CJ group. There were no failures up to 6 months after loading and there were 3 complications in the BB group and 3 complications in the CJ group (relative risk: 1.00, 95%CI from 0.22 to 4.49, P=1.0). The estimated difference between treatments in vertical defect bone gain was -0.15mm (95%CI from -0.65 to 0.35, P=0.5504) favoring the BB group, and the estimated difference between treatments in horizontal defect bone gain was -0.27mm (95%CI from -0.73 to 0.19, P=0.2461) favoring the BB group. There was no difference in complete closure of the defect, chair-time, pain after surgery and histologic analysis. A slight difference (0.24mm, P=0.0464) was detected in radiographic bone loss favoring CJ group.

Conclusions: No significant differences, except for radiographic bone loss, were observed in this randomised controlled trial comparing BB and CJ groups.

INTRODUCTION

Augmentation procedures at implant sites are divided into two broad categories: horizontal bone augmentation, which results in increasing recipient bone width in the bucco-oral direction and vertical bone augmentation when the focus is on increasing the height of the recipient bone in the apico-coronal direction (Esposito et al. 2009). Bone augmentation procedures may be carried out prior to implant placement (two-stage procedure) or simultaneously with implant placement (one-stage procedure) using various materials and techniques (Esposito et al. 2009). In one-stage horizontal bone augmentation, resorbable collagen barrier membranes in combination with a variety of graft materials, such as autogenous bone, allografts, xenografts, and alloplastic materials, are often used (Zitzmann et al. 1997, Merli et al. 2006, Schwarz et al. 2007, Schwarz et al. 2008, Chiapasco & Zaniboni 2009, Merli et al. 2013). In addition, the titanium implant surface characteristics may play a role in bone regeneration in dehiscence-type defects (Schwarz et al. 2010). There are several systematic reviews on horizontal bone augmentation (Esposito et al. 2009, Chiapasco & Zaniboni 2009, Jensen & Terheyden 2009, Clementini et al. 2012, Kojasteh et al. 2013, Kuchler & von Arx 2014). However, one-stage randomised controlled trials (RCTs) are scarce. The aim of this double-blind parallel randomised clinical trial is to compare Bio-Oss® and Bio-Gide® membrane (BB group) with Ceros-TCP® and Jason® membrane (CJ group) in a one-stage procedure for horizontal bone augmentation, in terms of: duration of surgery in minutes, failures, complications, patient pain, histomorphometric characteristics, clinical and radiographic bone level. In this report, the 6-month post-loading clinical follow-up will be assessed. This study is written in accordance with the Consort 2010 explanation and elaboration guidelines for reporting parallel group randomised trials (Moher et al. 2010).

MATERIALS AND METHODS

This was a mono-centre, double-blind clinical trial, with balanced randomization and parallel, two-group design. The 2 groups were composed of: 1. Bone mineral of bovine origin (Bio-Oss®, Geistlich Biomaterials AG, Wolhusen, Switzerland) and collagen porcine membrane (Bio-Gide®, Geistlich Biomaterials AG) (BB group) and: 2. Synthetic resorbable bone graft substitute made of pure β-tricalcium phosphate (Ceros-TCP®, Thommen Medical AG, Grenchen, Switzerland) and porcine pericardium collagen membrane (Jason®, Bottis AG, Bettlach, Switzerland) (CJ group). Eligible participants were adults, aged 18 or older, in need of implant treatment in at least one site with an expected horizontal osseous defect and tooth extraction at least 6 weeks prior to implant placement.

Inclusion criteria were:
- expected horizontal osseous defect requiring implant treatment in at least one site with horizontal osseous defect;
- patients 18 years old or older (completed skeletal growth);
- tooth extraction at least 6 weeks prior to bone augmentation surgery.

Exclusion criteria were:
- general contraindications to implant surgery;
- patients irradiated in the head and neck area;
- patients undergoing chemo- or immunosuppressive therapy over the previous 5 years;
- patients treated or undergoing treatment with intravenous amino-bisphosphonates;
- patients with poor oral hygiene and motivation;
- uncontrolled diabetes;
- pregnancy or lactating period;
- substance abusers;
- allergy to collagen;
- smoking more than 20 cigarettes per day, or the equivalent.

The study took place at the Clinica Merli, a private centre in Rimini (Italy). The dental office obtained the approval of the local authorities to conduct clinical study (protocol number 0134011). The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. An independent Ethics Committee (Ethical Committee IRST-IRCCS-Area Vasta Romagna) approved this clinical study (protocol number 4510/2013 1.5/161). The principal investigator has 20 years experience in dental implant surgery and dental implant prosthesis.

The implant placement was performed either as an early (between 6 weeks and 6 months after extraction) or a delayed procedure (more than 6 months after extraction). Before the intervention, baseline demographic and clinical characteristics were verified. An expert surgeon (M Merli) completed all the surgical procedures. Individual surgical guides were manufactured based on CBCT virtual planning and on diagnostic prosthetic set-up on study models. Patients subjected to local anesthesia alone received 2g Amoxicillin and Clavulanic Acid one hour prior to surgery. Patients subjected to intravenous sedation received 1g Ceftriaxone intravenously followed by Amoxicillin as above. Intravenous sedation was performed using fractioned administration of 0.5-1mg Midazolam and 0.5mg Atropin. The following analgesics were administered intravenously: 100mg Tramadol, 30mg Ketorolac and 4mg Betamethasone. Articaine with Epinephrine 1:100.000 was used as local anesthetic. Full thickness flaps were raised to fully expose the area to be regenerated after a mid-crestal incision and buccal releasing incisions when needed. The implant placement followed the submerged technique. Patients received Element RC Inicell® implants (Thommen Medical AG). The choice of the implant diameter and length was left to the surgeon's discretion. The manufacturer's instructions were followed. Implants lacking primary stability were replaced by implants with a larger diameter. Vestibular vertical defect length (DL) was measured as the linear distance from the implant shoulder to the deepest point of the first bone to implant contact. Horizontal defect width (DW) was measured as the widest linear mesio-distal dimension of the adjacent vestibular bone walls. Patients were randomised to receive either Bio-Oss/Bio-Gide or Ceros-TCP/Jason treatment system. The defects were filled with the bone substitute and autologous bone harvested during the implant insertion procedure. The regenerated area was covered with the membrane properly cut and fitted. The membrane was stabilized with titanium osteosynthesis tacks (Kalos, Nike®, Orbetello, Italy). If proper flap release and adaptation cannot be achieved with periosteal releasing incisions, a muscular dissection or a periosteal flap (periosteoplasty) was performed to allow a proper wound closure. Horizontal mattress sutures (4-0) plus single stitches (5-0) (Supramid®, Aesculap AG & CO.KG, Tuttlingen, Germany) were used Amoxicillin and Clavulanate 1g twice a day for 7 days and Ibuprofen 600mg twice a day for 2 days and then as needed was prescribed to all patients. Ice packs were given to the patients to be maintained for the first two-three hours after the surgical treatment. Patients were instructed to refrain from mechanical plaque removal in the area of implant placement for 1 week, to use chlorhexidine mouthrinse (0.12%) twice a day from the second postoperative day and to apply chlorhexidine gel to the wound area twice a day for 15 days. Patients were advised to avoid smoking during the prescribed recovery period. The abutment connection was made after 6 months of healing. A full thickness flap was reflected and the blind assessor measured vertical defect length (DL) and horizontal defect width (DW).

Two clinical cases are shown in Figg. 1-2.

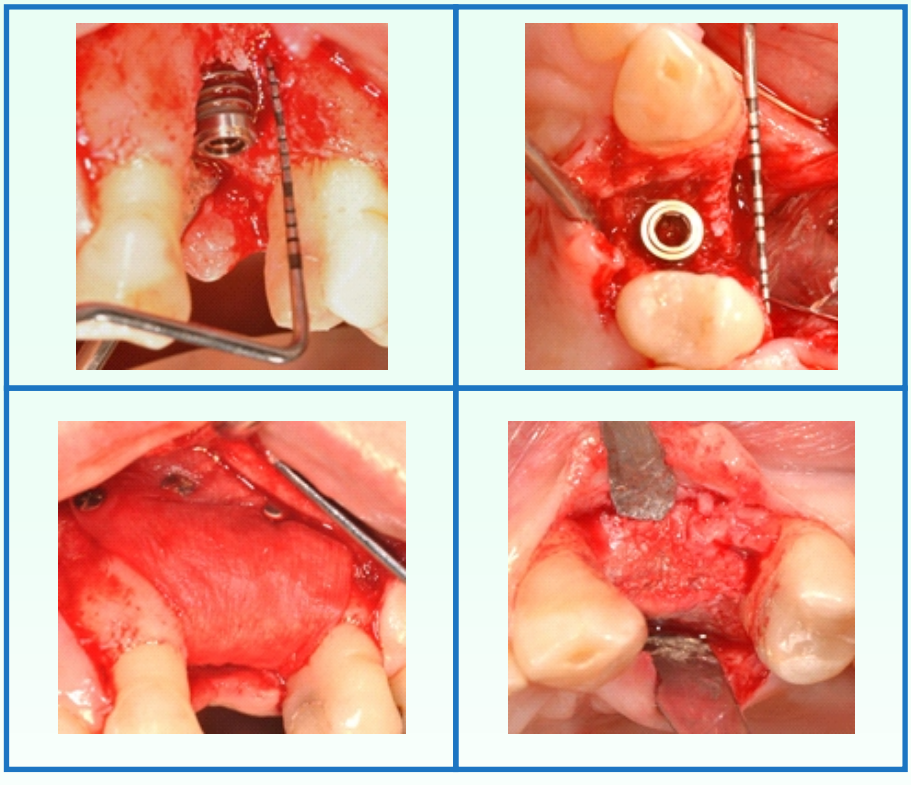

Figure 1. *BB group. From left to right: sequence of clinical images of pre- and post-regeneration surgery.*

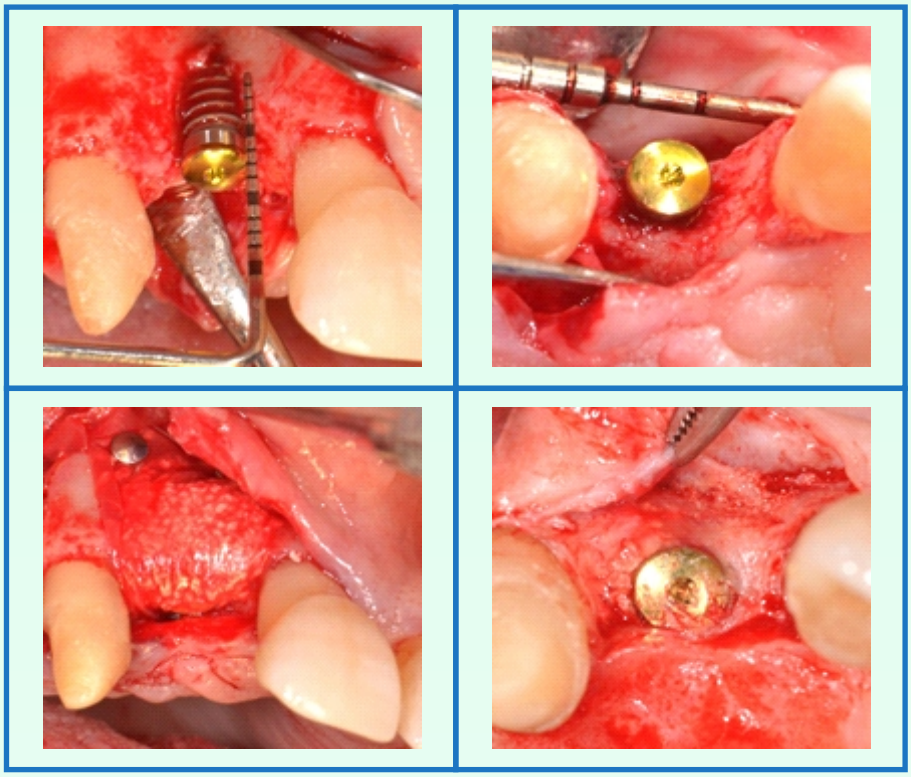

Figure 2. *CJ group. From left to right: sequence of clinical images of pre- and post-regeneration surgery.*

The application of the provisional prosthesis was performed after abutment connection and a definitive metal-ceramic prosthesis was placed 6 months post-loading. Outcome measurements were registered by an assessor blinded to the treatment administration (M Moscatelli). Primary outcome measures were: implant failure, complications at the augmented sites, clinical bone gain at the defect, and complete closure of the defect. Bone gain was measured with the difference between vertical defect length (DL) at surgery and after 6 months and with the difference between horizontal defect width (DW) at surgery and after 6 months. DL was measured as linear distance from the implant shoulder to the deepest point of the first bone-to-implant contact and DW was measured as the widest linear mesio-distal dimension of the adjacent vestibular bone walls. Complete closure of the defects was assigned a value of 1 only in cases where both vertical and horizontal defects were zero (measurements included the polished portion of the implant) in every implant per patient. Otherwise the closure of the defect was considered incomplete and the value assigned was 0. Chair-time was registered from implant preparation to the completion of suturing. VAS for patient pain was registered immediately after surgery, after 1 week and after 2 weeks. The VAS was from 0 (no pain) to 10 (worst possible pain). Peri-implant marginal bone level change was assessed on periapical intraoral radiographs taken with the parallel technique at surgery and 6 months after loading. The digitized radiographs were examined using commercially available software (Immagine®, Dental Trey Srl, Fiumana-Predappio, Italy) by one examiner (MG). The examiner was calibrated and subjected to an intra-rater agreement test. Reference points for the linear measurements were: the coronal margin of the implant collar and the most coronal point of bone-to-implant contact. Implants with bone up to the coronal margin of the implant collar were given the zero value. The mesial and distal sites were averaged for each implant and implants were averaged per patient. The radiographic measurements were relativized considering the length of the implants used according to the formula: Rx length x Real implant/Rx implant length. For the first ten patients treated a biopsy was taken in the regenerated area at abutment connection and histomorphometric analyses were performed. These bone biopsies were retrieved using a trephine bur and fixed in 10% buffered formalin. The specimens were dehydrated in an ascending series of alcohol rinses and embedded in a glycolmethacrylate resin (Techonovit 7200 VLC; Kulzer, Wehrheim, Germany). After polymerization, the specimens were sectioned along their longitudinal axis with a high-precision diamond disk and ground to approximately 40µm with a specially designed grinding machine (Remet, Casalecchio di Reno, Italy).

The undecalcified ground sections were stained with acid fuchsine and toluidine blue staining. The slices were observed under normal transmitted light with a light microscope (Nikon Eclipse, Nikon, Tokyo, Japan). The histomorphometric analysis was carried out using a light microscope (Nikon Eclipse, Nikon, Tokyo, Japan) connected to a high-resolution video camera. This optical system was associated to a histometry software package with image-capturing capabilities (Image-Pro Plus 4.5; Media Cybernetics Inc., Milano, Italy).The variables investigated with the biopsies examination were percentages of new bone, mineralized native tissue, residual graft and marrow space/soft tissue were calculated. Sample size determination was performed to detect a difference between treatments of 1 mm in bone gain measured between vertical defect length (DL) at surgery and after 6 months. Using a standard deviation of 1.16 mm in agreement with the study of Jung et al. (2009) with a two-side 5% significance level and power of 80%, a sample size of 50 patients (25 per group) was necessary, given an anticipated drop-out rate of 10%. For allocation of the participants, a computer-generated list of random numbers was used. A blocked randomisation was applied to include 25 patients in each treatment group. The allocation sequence was concealed from the researcher (MN) enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. The envelope was opened only after implant placement. Whereas the surgeon was aware of the allocation arm, patients and the outcome assessor were kept blinded to the allocation. The complications were registered and treated by the surgeon in a non-blinded mode.

Descriptive statistics were performed using mean and standard deviation for quantitative data and frequency and percentage for qualitative data. The statistical unit of the analysis was the patient. Measures at implant site were averaged and presented at patient level. Analysis of covariance (ANCOVA) was performed for DL, DW and radiographic bone level change. Values at baseline were the covariates.

The qualitative variables implant failure, complications and complete closure of the defect were subjected to the Fisher exact test. Relative risks were used to estimate the results. t-tests were performed for chair-time, VAS pain immediately after surgery, VAS pain after 1 week and VAS pain after 2 weeks. The histological data was investigated using the compositional data analysis (Aitchison 1986). Descriptive statistics was performed using for each arm the centre (the geometric mean of the components). Three t-test analyses were conducted using the treatment (Bio-Oss/Bio-Gide versus Ceros-TCP/Jason) as explicative variable and the additive logratio transformation (ALR) of the composition as outcome variables. In the ALR transformation the divisor of the logratio was the percentage of marrow space/soft tissue in the specimen. The numerator of the logratios were the percentage of new bone, the percentage of the mineralized native tissue and the percentage of the residual graft (Faes et al. 2011). The statistical software were CoDaPack v. 2 (Department of Computer Science and Applied Mathematics of the University of Girona, Spain) and JMP v. 11 (SAS Institute Inc., Cary, NC, USA).

RESULTS

All 50 randomized patients received treatment as allocated and there were no discontinued patients until 6 months after loading. Twenty-five patients with 32 implants were allocated to the BB group and 25 patients with 29 implants to the CJ group. There was only one deviation from the protocol. One patient from the CJ group had abutment connection 12 months after treatment for health issues not related to the study procedures or the implant healing. Baseline demographic and clinical characteristics for each group are reported in Table 1. No differences were detected at baseline between the two groups. The analysis was intention-to-treat and involved all the patients who were randomly assigned to the treatments. Failures, complications, chair-time, VAS, vertical and horizontal defect at re-entry, bone gain and frequency of complete closure of the defect were reported in Table 2. There were no failures and no membrane was removed. There were 3 complications in BB group and 3 complications in the CJ group. The complications in the BB group were: one minor complication consisted of a dehiscence of the mucosa 90 days after surgery; another, the presence of purulent exudate 60 days after surgery and the third in a patient with tingling sensation and hyposensitivity of the treated area 7 days after surgery. The complications in the CJ group were: one minor complication was a dehiscence of the mucosa 30 days after surgery, and two complications in patients with presence of purulent exudate 14 days after surgery.

Table 1. *Baseline demographic and clinical characteristics.*

Variable	BB Group N=25	CJ Group N=25
Age (SD) [min; max]	56.0 (13.0) [31; 76]	53.4 (12.4) [30; 76]
Gender (female)	17 (68%)	16 (64%)
Smokers	4 (16%)	3 (12%)
Maxillary	4 (16%)	11 (44%)
Implant length mm (SD)	10.9 (1.9)	11.2 (1.9)
Implant diameter mm (SD)	4.0 (0.3)	4.1 (0.3)
Vertical defect T0 mm (SD)	4.9 (1.8)	5.3 (1.9)
Horizontal defect T0 mm (SD)	3.4 (1.0)	4.0 (1.4)
Rx baseline mm (SD)	0.07 (0.13)	0.12 (0.27)

BB: Bio-Oss/Bio-Gide group; CJ: Ceros-TCP/Jason group; SD: Standard Deviation; min: minimum; max: maximum.

Table 2. *Failures, complications, chair-time, VAS, vertical and horizontal defect at re-entry, bone gain and frequency of complete closure of the defect.*

Variable	BB Group N=25	CJ Group N=25	P-value
Failures	0	0	
Complications ♣	3 (12%)	3 (12%)	1.0
Chair-time minutes (SD) ♠	49.6 (12.3)	45.2 (19.9)	0.3524
VAS Post-op (SD) ♠	0.8 (1.4)	0.6 (1.1)	0.5644
VAS 1 week (SD) ♠	0.8 (1.4)	0.5 (0.7)	0.5074
VAS 2 weeks (SD) ♠	0.7 (1.4)	0.6 (1.1)	0.6950
Vertical defect T1 mm(SD) ♥	0.4 (0.8)	0.5 (0.9)	0.5504
Horizontal defect T1 mm (SD) ♥	0.3 (0.6)	0.5 (0.9)	0.2461
Vertical bone gain mm (SD) ♥	4.5 (2.0)	4.7 (2.4)	0.5504
Horizontal bone gain mm (SD) ♥	3.1 (1.2)	3.5 (1.7)	0.2461
Complete closure of the defect ♣	17 (68%)	15 (60%)	0.7688
Rx bone level 6month post-loading mm (SD) ♥	0.84 (0.37)	0.66 (0.55)	0.0464
Rx bone loss mm (SD) ♥	-0.77 (0.36)	-0.54 (0.45)	0.0464

BB: Bio Oss/Bio-Gide group; CJ: Ceros-TCP/Jason group SD: Standard Deviation. ♠ t-test; ♣ Fisher exact test; ♥ ANCOVA test.

The dehiscence and the purulent exudates were treated with chlorhexidine gel 0.5%, chlorhexidine rinse 0.12% and Amoxicillin/Clavulanic Acid for 7 days. The tingling sensation and hyposensitivity was treated with Gabapentin and B12-vitamin for 20 days. All the symptoms of complications regressed to disappear within about 10 days. There was no difference in complications between treatments; the relative risk was 1.00 (95%CI from 0.22 to 4.49, P=1.0). Vertical bone gain was 4.5mm for the BB group and 4.7mm for the CJ group. Considering the baseline value as a covariate, the estimate difference between treatments in vertical bone gain was -0.15mm (95%CI from -0.65 to 0.35mm, P=0.5504) favoring BB group. Horizontal bone gain was 3.1mm for the BB group and 3.5mm for the CJ group. Considering the baseline values for each group respectively as a covariate, the estimate difference between treatments in horizontal bone gain was -0.27mm (95%CI from -0.73 to 0.19mm, P=0.2461) favoring BB group. Complete closure of the defects was obtained in 17 patients in BB group and 15 patients in CJ group. The relative risk was 0.88 (95%CI from 0.58 to 1.34, P=0.7688) favoring the BB group. Chair-time was 49.6 minutes in the BB group and 45.2 minutes in the CJ group. The estimate difference was -4.4 minutes (95%CI from -13.8 to 5.0 minutes, P=0.3524) favoring the CJ group. Immediately post-surgery VAS pain was 0.8 in the BB group and 0.6 in the CJ group. The estimated difference was -0.2 (95%CI from -0.9 to 0.5, P=0.5644) favoring the CJ group. One week post-surgery VAS pain was 0.8 in the BB group and 0.5 in the CJ group. The estimated difference was -0.2 (95%CI from -0.8 to 0.4, P=0.5074) favoring the CJ group. Two weeks post-surgery VAS pain was 0.7 in the BB group and 0.6 in the CJ group. The estimate difference was -0.1 (95%CI from -0.9 to 0.6, P=0.6950) favoring the CJ group. Radiographic bone loss was 0.77mm for the BB group and 0.54mm for the CJ group. Considering the baseline value as a covariate, the estimate difference between treatments in radiographic bone loss was 0.24mm (95%CI from 0.0004 to 0.47mm, P=0.0464) favoring CJ group. The histological data were analyzed using the percentage of new bone, mineralized native bone, residual graft and marrow spaces/soft tissue. The centres (geometrical means) were reported in Table 3. Logratio means, standard deviations, differences between treatments, confidence intervals of the differences and p-values are reported in Table 4. The comparisons were all not significant but the difference between logratios involving residual graft approaches significance (P = 0.0759). The percentage of residual graft using the marrow spaces and soft tissue as reference tended to be greater in the Ceros-TCP/Jason group.

Table 3. *Histologic analysis. Centres of the groups.*

Variable	BB Group N=5 Centre	CJ Group N=5 Centre
New Bone %	21	20
Mineralized Tissue %	29	24
Residual Graft %	22	28
Marrow Spaces/Soft Tissue %	27	28

Table 4. Histologic analysis. t-test of the logratio.

	BB Group N=5 Mean (SD)	CJ Group N=5 Mean (SD)	Difference [CI95%]	P-value
Log(NB/MS)	-0.27 (0.29)	-0.35 (0.35)	0.09 [-0.39; 0.56]	0.6809
Log(MT/MS)	0.07 (0.28)	-0.18 (0.38)	0.26 [-0.23; 0.74]	0.2591
Log(RG/MS)	-0.20 (0.12)	0.002 (0.18)	-0.20 [-0.43; 0.03]	0.0759

NB: new bone; MT: mineralized native tissue; RG: residual graft; MS: marrow space/soft tissue.
BB: Bio-Oss/Bio-Gide group; CJ: Ceros-TCP/Jason group. SD: Standard Deviation; CI95%: Confidence Interval 95%.

DISCUSSION

The aim of this short-term follow-up RCT was to clinically compare the combined treatment with Bio-Oss/Bio-Gide and Ceros-TCP/Jason in one-stage procedures for horizontal bone augmentation in dehiscence-type defects at implant sites. No difference between treatment was detected for implant failures, complications, bone gain, complete closure of the defect, chair-time, VAS-pain registered immediately after surgery and after one and two weeks and histologic data. Instead, a little difference was detected for radiographic marginal bone change 6 months after loading. To our knowledge this is the first RCT that compares Bio-Oss/Bio-Gide membrane and Ceros-TCP/Jason membrane in a one-stage procedure for horizontal bone augmentation, hence there are no reference studies in literature. No implant failures were observed and no membrane was removed. The complications were only present in 12% of the treated patients and their treatment was successful. In addition, VAS related pain was very low in the two groups, indicating the safeness of the implemented devices. This is an important finding considering that a recent study was discontinued early because unacceptable safety issues arose with severe infections and soft tissue dehiscence in the sites treated with a new cross-linked membrane (Annen et al. 2011). There were no differences in clinical bone gain and in complete closure of the defect between the two groups. The values are comparable to those of another similar RCT (Van Assche et al. 2013). Radiographic bone loss 6 months after loading was slightly higher in BB group. The difference of this secondary outcome variable (0.24 mm) was statistically significant but clinically negligible and should be verified at 1 and 3 year post-loading follow-ups. The histologic analysis was performed in 10 patients. After 6 months from the augmentation procedure, the Bio-Oss residual graft constituted 22% of the augmented tissue and new bone formation was 21%. Other studies reported about 30% of residual graft after 6 to 9 months of sinus augmentation (Yildirim et al. 2000, Simunek et al. 2008). The histomorphometric analysis in the Bio-Oss/Bio-Gide arm of an RCT on peri-implant horizontal defect showed 28.9% of residual graft after 6 months of follow-up (Annen et al. 2011). On the contrary, in this study, the β-TCP residual graft still constituted 28% of the augmented tissue and new bone formation was 20%. Another study reported 39% of residual graft after 9 months of sinus augmentation (Simunek et al. 2008). A limit of this RCT is the short follow-up. Important variables such as implant and prosthetic failures, subjective satisfaction and aesthetic concern will be investigated up to 3-year post-loading follow-up. An expert surgeon with more than 20 years of experience in implant surgery performed all the interventions and this should be considered when extrapolating the results from this trial to other settings. In conclusion, except for radiographic bone level, the comparisons between the Bio-Oss/Bio-Gide system and the Ceros-TCP/Jason system in a one-stage procedure for horizontal bone augmentation were all not significant. Both treatments can be used in routine clinical practice.

ACKNOWLEDGMENTS

The authors express their deepest appreciation to Heather Dawe and Marco Bonfini for their kind contribution in editing the manuscript.
Thommen Medical AG provided the implants as well as the Jason membrane and Ceros-TCP free of charge.

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