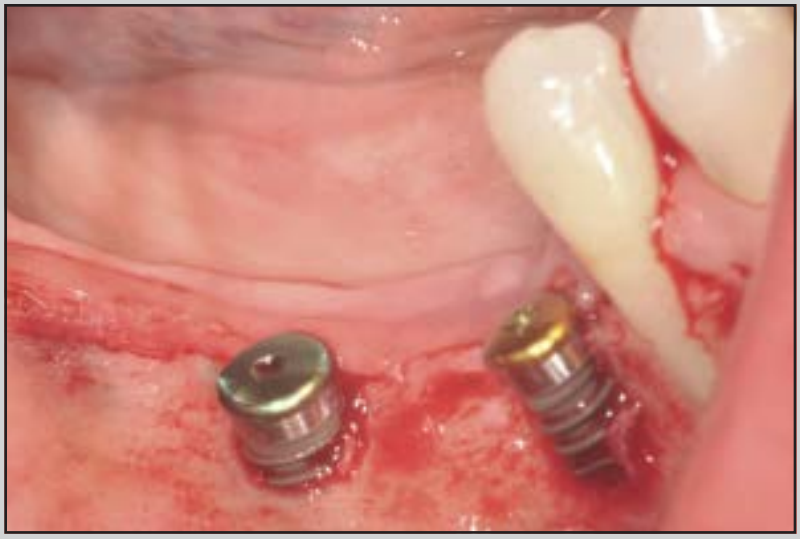

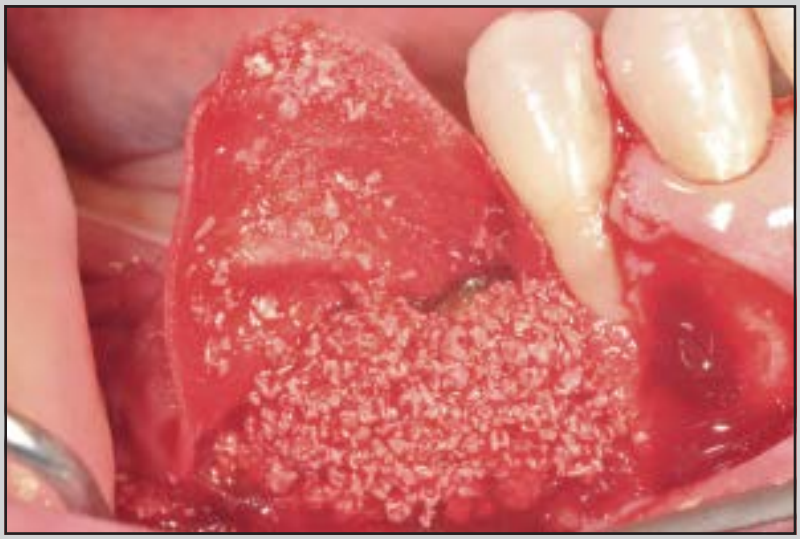

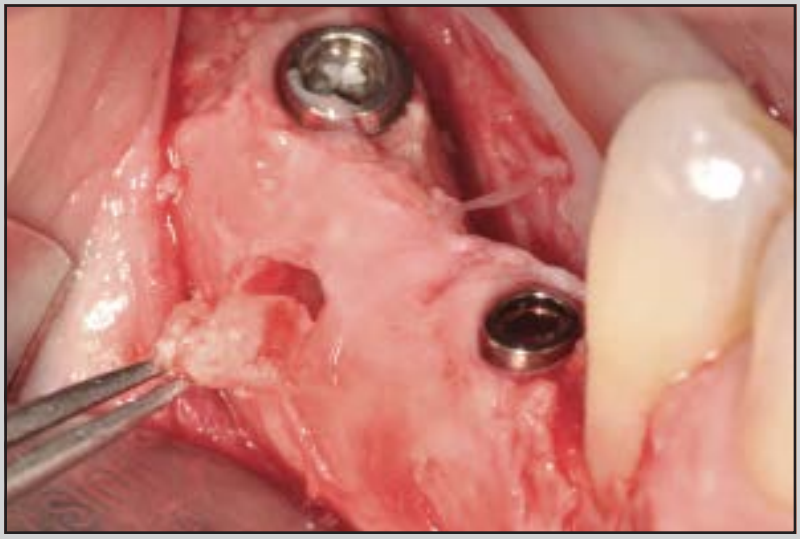

Membranes and Bone Substitutes in a One-Stage Procedure for Horizontal Bone Augmentation: A Histologic Double-Blind Parallel Randomized Controlled Trial

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The aim of this histologic, double-blind, parallel, randomized controlled trial was to compare anorganic bone mineral-collagen membranes (BB) and beta-tricalcium phosphate-pericardium collagen membranes (CJ) in a one-stage procedure for horizontal bone augmentation. A biopsy was performed in the regenerated area at abutment connection 6 months after surgery. Five patients were assigned and treated with the BB combination and five patients were treated with the CJ combination. At abutment connection, 6 months after grafting, no significant differences were evident in the histomorphometric comparisons, even if the percentage of residual graft, using the marrow spaces and soft tissue as a reference, tended to be greater in the CJ group (P = .0759).
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Implant therapy in some patients may require bone augmentation to improve the anatomic situation of the implant site. These reconstructive procedures may be carried out before implant placement (two-stage procedure or staged approach) or simultaneously with implant placement (one-stage procedure or simultaneous approach), using various biomaterials and techniques.[1]

The simultaneous approach is the technique preferred by the patient and the clinician alike, because it reduces treatment time and cost.[2]

Augmentation procedures are divided into two broad categories: horizontal bone augmentation, in which the technique is aimed at making the recipient bone wider in the bucco-oral direction to receive dental implants of adequate diameter, and vertical bone augmentation, in which the technique focuses on increasing the height of the recipient bone to receive implants of adequate length.[1]

Common techniques introduced for horizontal bone augmentation are guided bone regeneration, ridge splitting and expansion, and block grafting of either autogenic or allogenic origin.[3]

In one-stage horizontal bone augmentation, barrier membranes in combination with various graft materials, such as autogenous bone,

allografts, xenografts, and alloplastic materials, are often used.[4–8] In addition, the titanium implant surface characteristics may play a role in bone regeneration in dehiscence-type defects.[9]

Several systematic reviews have been published on horizontal bone augmentation,[1,2,7,10–12] however, in humans, one-stage randomized controlled trials (RCTs) are scarce. These studies compared the use of different membranes[13–17] or compared regeneration with membranes vs the use of biomaterial only,[18] but histologic analysis was rarely performed.

An earlier split-mouth RCT comparing resorbable and nonresorbable membranes showed no difference in defect reduction.[13]

Another RCT compared the amount of bone fill using a cross-linked collagen membrane (10806 Geistlich Biomaterials) and a native collagen membrane (Bio-Gide, Geistlich Biomaterials) for the treatment of dehiscence-type defects at titanium implant insertion sites.[16] The study was discontinued early, after having surgically treated 9 split-mouth patients, because of unacceptable safety issues caused by severe infection related to the use of cross-linked membranes.[16] The bone fill was significantly greater in the native collagen membrane but the histologic data showed only some trends and did not reach the level of statistical significance.[16] In particular, the xenogenic bone substitute mineral occupied an average area of 48.4% at the cross-linked membrane sites and 28.9% at the native collagen membrane sites.[16]

Currently, no RCTs exist that compare the widely used biomaterial system (collagen porcine membrane [Bio-Gide] and a natural bone mineral of bovine origin [Bio-Oss, Geistlich Biomaterials]) with another promising system consisting of a multilayer, porcine pericardium natural collagen membrane (Jason, Bottis) and a synthetic bone graft substitute made of pure beta-tricalcium phosphate (TCP; Ceros TCP, Thommen Medical) for one-stage horizontal bone augmentation. This comparison was performed only in a previous split-mouth case report in which both therapeutic approaches have proved favorable for covering initially exposed implant threads.[19]

The aim of this double-blind, parallel, randomized controlled trial was to compare Bio-Gide membrane–Bio-Oss (BB) and Jason membrane–Ceros TCP (CJ) in a one-stage procedure for horizontal bone augmentation. This article exclusively reports the histologic results.

This study is written in accordance with the Consort 2010 explanation and elaboration guidelines for reporting parallel group RCTs.[20]

Method and materials

Trial design

This was a monocenter, double-blind clinical trial, with balanced randomization and a parallel two-group design. The two groups included: (1) collagen porcine membrane and bone mineral of bovine origin (group BB); and (2) porcine pericardium collagen membrane and synthetic resorbable bone graft substitute made of pure beta-TCP (group CJ).

Eligibility criteria

Inclusion criteria were:

- Expected horizontal osseous defect requiring implant treatment in at least one site with horizontal osseous defect
- Eighteen years of age or older (completed skeletal growth)
- Tooth extraction at least 6 weeks before bone augmentation surgery

Exclusion criteria were:

- General contraindications to implant surgery
- Radiation to the head and neck area
- Chemo or immunosuppressive therapy over the previous 5 years
- Current or previous treatment with intravenous amino-bisphosphonates
- Poor oral hygiene and motivation
- Uncontrolled diabetes
- Pregnancy and lactating period
- Substance abuse
- Allergy to collagen
- Smoking more than 20 cigarettes per day or equivalent

Setting, locations, and ethics

The study took place at the Clinica Merli, a private center in Rimini, Italy. The dental office obtained the

approval of the local authorities to conduct clinical studies (protocol number 0134011).

The study was conducted in accordance with the ethical principles of 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.

Interventions

The implant placement was performed either as an early (6 weeks–6 months after extraction) or a delayed procedure (> 6 months after extraction). Baseline demographic and clinical data were verified before surgery. An expert surgeon performed all the surgical procedures.

Surgical stents with hollow titanium cylinders guiding implant placement to the ideal position for prosthetic rehabilitation were used for each patient. Stents were developed from study models taken with an individualized tray based on a cone beam computed tomographic scan of the atrophic area.

Patients undergoing local anesthesia alone received 2 g of amoxicillin-clavulanic acid 1 hour before surgery. Patients undergoing intravenous sedation received 1 g of ceftriaxone intravenously followed by amoxicillin as before.

Intravenous sedation was performed using fractioned administration of 0.5 to 1 mg midazolam and 0.5 mg atropine. The following analgesics were administered intravenously: 100 mg tramadol, 30 mg ketorolac, and 4 mg betamethasone. Articain with adrenalin 1:100.000 was used as local anesthetic.

A crestal incision and releasing incisions, when necessary, were performed and full-thickness flaps were raised to fully expose the area to be regenerated.

Implant placement followed the submerged technique approach. Patients received Element RC Inicell implants (Thommen Medical). 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 to be replaced by implants with a larger diameter.

Vestibular vertical defect length (DL) was measured as a 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 mesiodistal dimension of the adjacent vestibular bone walls.

Patients were randomized to receive either Bio-Oss and Bio-Gide membrane or Ceros TCP and Jason membrane. The defects were filled with the bone substitute and autologous bone harvested during the implant insertion procedure. Using a twist drill at low speed, marrow space was opened without irrigation, the autologous bone particles were left in situ, and the defect was then filled with the bone substitute. The percentage of autologous bone in the graft can be approximated from 5% to 10%.

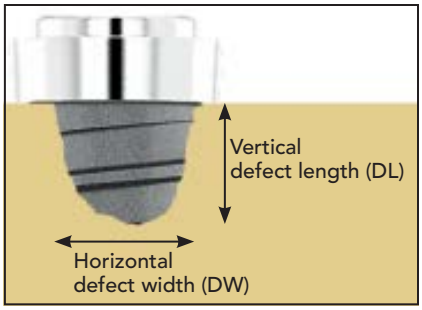


Fig 1 *Buccal view: horizontal defect.*

If correct flap release and adaptation could not be achieved with releasing incisions in the periosteum, a periosteal flap was reflected and sutured to allow proper wound closure (periosteoplasty). Horizontal mattress sutures (4-0) plus single stitches (5-0) (Supramid, Aesculap) were used.

Ibuprofen 600 mg twice a day for 2 days and then as needed was prescribed to all patients. Ice packs were given to the patients. Patients were instructed to refrain from mechanical plaque removal in the area of implant placement for 1 week, to use chlorhexidine mouth rinse (0.12%) twice a day from the third postoperative day and to apply chlorhexidine gel on 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 mucoperiosteal full-thickness flap was reflected and the blind assessors measured vertical DL and horizontal DW (Fig 1).

A case from the control group and test group are shown in Figs 2 and 3, respectively.

Histologic analysis

A biopsy was performed in the regenerated area at the abutment connection on the first 10 patients of this study. Histologic and histomorphometric analyses were performed. In detail, bone biopsy specimens of the augmented tissue were retrieved using a trephine bur and immediately fixed in 10% buffered formalin and processed for histologic and histomorphometric analysis. The specimens were dehydrated in an ascending series of alcohol rinses and embedded in a glycolmethacrylate resin (Technovit 7200 VLC, Kulzer). After polymerization, the specimens were sectioned along their longitudinal axis with a high-precision diamond disk and ground to approximately 40 mm with a specially designed grinding machine (Remet). The undecalcified ground sections were stained with acid fuchsin and toluidine blue stain. The slides were observed under normal transmitted light with a light microscope (Nikon Eclipse). The histomorphometric analysis was carried out using a light microscope connected to a high-resolution video camera; this optical system was associated with a histometry software package with image-capturing capabilities (Image-Pro Plus 4.5, Media Cybernetics).

Outcome measures

This article exclusively reports on the histologic data of the first 10 patients included in this RCT. The clinical data on the full sample size will be reported in a forthcoming publication.

Percentages of new bone, mineralized native tissue, residual graft, and marrow space/soft tissue were calculated. Outcome measurements were registered by an assessor blinded to the treatment administered.

Sample size

To detect a difference between treatments of 1 mm in bone gain measured between vertical DL at surgery and after 6 months (Fig 1) (standard deviation of 1.16 mm in agreement with the study of Jung et al[14]) with a two-sided 5% significance level and power of 80%, a sample size of 50 patients was necessary, given an anticipated dropout rate of 10%. This histologic study is based on the fraction of 10 patients who underwent biopsy.

Random sequence

For allocation of the participants, a computer-generated list of random numbers was used. A blocked randomization was used: 25 patients were included in each treatment group. In addition, of the first 10 patients, 5 were included in each treatment group.

Allocation concealment

The allocation sequence was concealed from the researcher (M.N.) enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes. The envelope was opened by the surgeon only after implant placement.

Blinding

Although the surgeon was aware of the allocation arm, the patients and the outcome assessor were blinded to the allocation. Although unaware of the therapy used, the histologic assessor (A.M.) was able to recognize the grafting material used.

Statistical methods

The histologic data were investigated using the compositional data analysis.[21] Compositional data consist of vectors whose components are the proportion or percentage of the whole. Their peculiarity is that their sum is constrained to be some constant, equal to 1 for proportion or 100 for percentage. In this histologic study, the sum of the percentages of new bone, mineralized native tissue, residual graft, and marrow space/soft tissue is always 100. The traditional statistical analysis of these data is biased and a peculiar analysis, the compositional data analysis, is advocated.[21,22]

Descriptive statistics was performed using the center (the geometric mean of the components) for each arm.

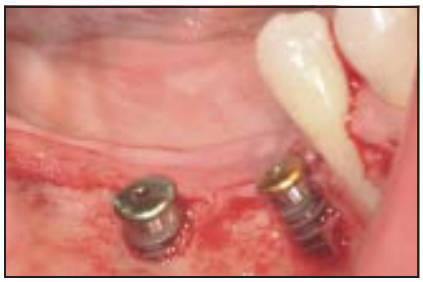


Fig 2a *Bio-Gide–Bio-Oss (BB) group. Prereconstructive lateral view with exposed implant threads.*

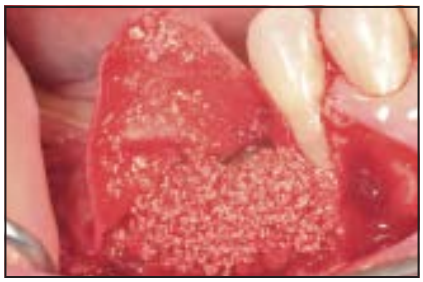


Fig 2b *Clinical photograph of the area subjected to reconstructive treatment (Bio-Oss combined with Bio-Gide).*

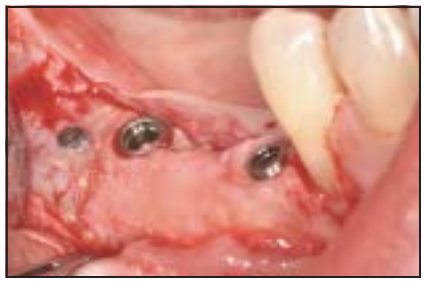


Fig 2c *Lateral view of the peri-implant regenerated bone at the second surgical phase.*

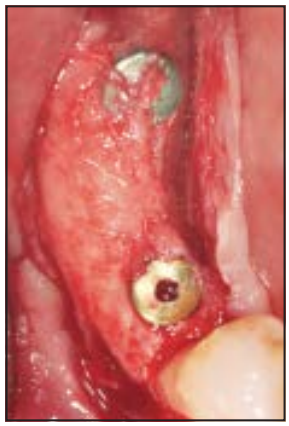
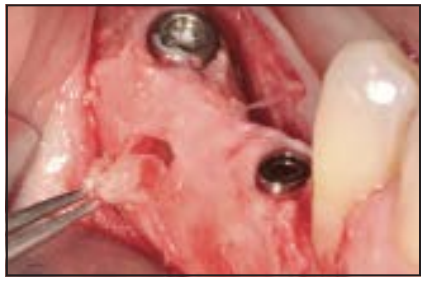


Fig 2d *Occlusal view of the peri-implant regenerated bone at the second surgical phase.*

Fig 2e *Detail of the bioptic sample.*



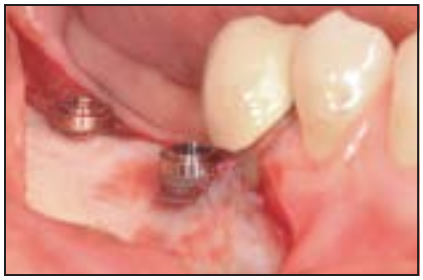


Fig 3a *Jason membrane–Ceros TCP (CJ) group. Prereconstructive lateral view with exposed implant threads.*

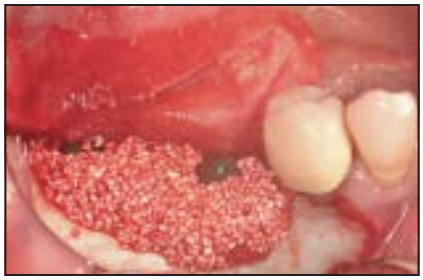


Fig 3b *Image of the area subjected to reconstructive treatment (Ceros-TCP combined with Jason).*

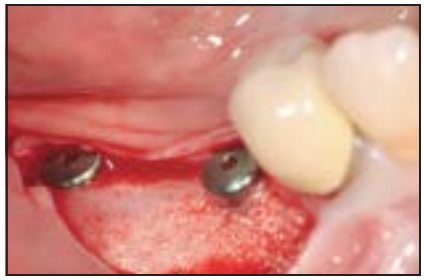


Fig 3c *Lateral direct view of the peri-implant regenerated bone at the second surgical phase.*

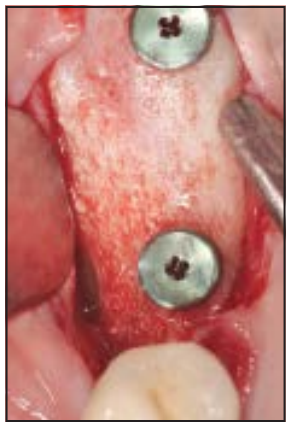


Fig 3d *Occlusal view of the peri-implant regenerated bone at the second surgical phase.*

Fig 3e *Detail of the bioptic sample.*

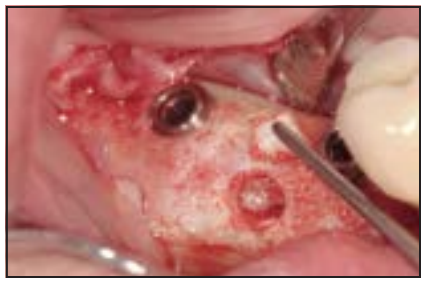


Table 1 Baseline characteristics

Variable	BB (n = 5)	CJ (n = 5)
Mean (SD) age (y)	56.4 (8.3)	62.0 (10.8)
Women, n (%)	4 (80%)	4 (80%)
Smoking status, n (%)	1 (20%)	0 (0%)
No. of implants	8	6
Maxillae, n (%)	0 (0%)	2 (40%)
Mean (SD) baseline vertical defect length (mm)	4.2 (0.9)	5.0 (1.4)
Mean (SD) baseline horizontal defect width (mm)	3.6 (0.5)	5.1 (2.2)
Mean (SD) vertical defect length at 6 mo (mm)	0.7 (1.3)	0.4 (0.5)
Mean (SD) horizontal defect width at 6 mo (mm)	0.5 (0.9)	0.5 (0.7)

BB = Bio-Oss and Bio-Gide group; CJ = Ceros TCP and Jason group; SD = standard deviation.

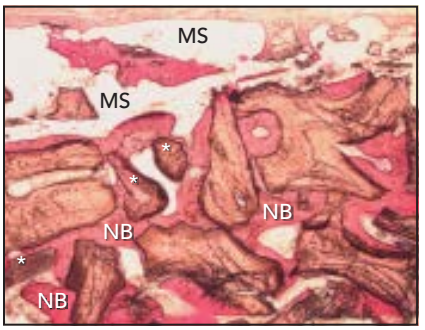


Fig 4a *Histologic image of the regenerated area using Bio-Oss and Bio-Gide (BB group). In the regenerated site, new bone (NB) formation was evident and residual grafting particles of Bio-Oss were recorded (asterisks) (toluidine-blue and acid fuchsin stain; original magnification ×5). Marrow spaces (MS) are also visible.*

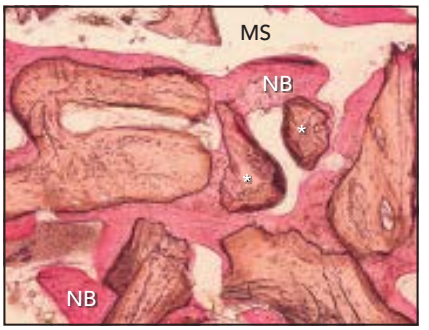


Fig 4b *Low-magnification view of an area regenerated using Bio-Oss and Bio-Gide (BB group). Residual grafting particles (asterisks) were evident and surrounded by newly formed bone (NB) (toluidine-blue and acid fuchsin stain; original magnification ×5). Marrow spaces (MS) are also visible.*

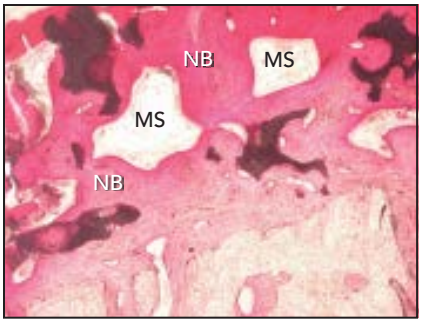


Fig 5a *Histologic view of the area regenerated using CerosTCP and Jason (CJ group). The analysis revealed the presence of residuals of beta-tricalcium phosphate (asterisks) surrounded by new bone (NB) (toluidine-blue and acid fuchsin stain; original magnification ×5). Marrow spaces (MS) are also visible.*

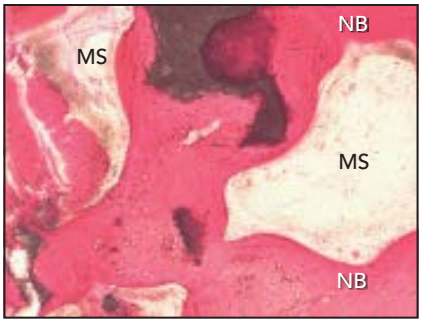


Fig 5b *Histologic image of the bone core biopsy specimens from the area regenerated using Ceros and TCP Jason membrane showing the presence of beta-tricalcium phosphate (asterisks) surrounded only partially by new bone (NB) (toluidine-blue and acid fuchsin stain; original magnification ×5). Marrow spaces (MS) are also visible.*

Three *t* test analyses were conducted using the treatment (Bio-Gide and Bio-Oss vs Jason and Ceros TCP) as the explicative variable and the additive logratio transformation of the composition as outcome variables. In the additive logratio transformation, the divisor of the logratio was the percentage of marrow space/soft tissue in the specimen. The numerator of the logratios were the percentages of new bone, mineralized native tissue, and residual graft.[22]

The statistical software used were CoDaPack version 2 (Department of Computer Science and Applied Mathematics of the University of Girona, Spain) and JMP version 11 (SAS Institute).

Results

This histologic study was performed on the first 10 patients enrolled in the RCT. All 10 patients were analyzed and there were no drop-outs. Five patients were assigned and treated with the Bio-Oss and Bio-Gide membrane and five patients were assigned and treated with the Ceros TCP and Jason membrane CJ.

Baseline information is presented in Table 1. Vertical and horizontal defects at the 6-month follow-up are reported in Table 1. These data will be analyzed and described in a forthcoming publication.

Results of the histologic analysis revealed bone remodeling in which the newly formed bone was already well organized with spotted regions, and grafted bone particles were detectable both in the BB and CJ groups (Figs 4 and 5).

The histologic data were analyzed using the percentage of new bone, mineralized native bone, residual graft, and marrow spaces/soft tissue. The individual patient data and the centers for these compositions are shown in Fig 6. The centers (geometric means) are also shown in Table 2.

Log ratio means, standard deviations, differences between treatments, confidence intervals of the differences, and *P* values are reported in Table 3.

The differences were all not significant, but the difference between logratios involving residual graft approached significance (*P* = .0759). The percentage of residual graft using the marrow spaces and soft tissue as reference tended to be greater in the CJ group.

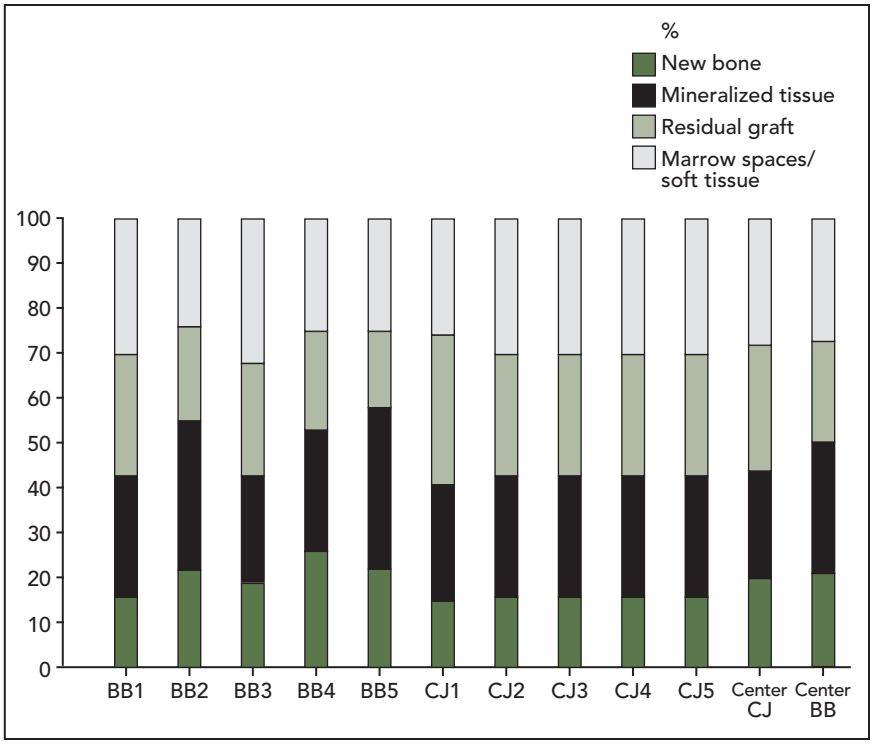


Fig 6 *Bar plot of the composition of histologic specimens. BB = Bio-Oss and Bio-Gide group; CJ = Ceros TCP and Jason group.*

Discussion

The aim of this RCT was to perform a histomorphometric comparison of Bio-Oss/Bio-Gide membrane and Ceros TCP/Jason membrane in a one-stage procedure for horizontal bone augmentation.

Bio-Gide is a porcine collagen membrane frequently used in combination with Bio-Oss, which consists of granules made of deproteinized bovine bone matrix. The Jason membrane is a porcine pericardium collagen membrane that can be used for guided bone regeneration in periimplant dehiscence-type defects.[19] In this study, Jason membrane was used in combination with Ceros TCP, a resorbable, synthetic beta-TCP with pore size of 100 to 500 µm.

Table 2 **Centers of the groups**

Variable	BB group center	CJ group center
New bone (%)	21	20
Mineralized tissue (%)	29	24
Residual graft (%)	22	28
Marrow spaces/soft tissue (%)	27	28

BB = Bio-Oss and Bio-Gide group; CJ = Ceros TCP and Jason group.

Table 3 **Results of *t* test of the log ratio**

	Mean (SD)			
	BB group (n = 5)	CJ group (n = 5)	Difference (95% CI)	*P*
Log (NB/MS)	–0.27 (0.29)	–0.35 (0.35)	0.09 (–0.39–0.56)	.6809
Log (MT/MS)	0.07 (0.28)	–0.18 (0.38)	0.26 (–0.23–0.74)	.2591
Log (RG/MS)	–0.20 (0.12)	0.002 (0.18)	–0.20 (–0.43–0.03)	.0759

SD = standard deviation; BB = Bio-Oss and Bio-Gide group; CJ = Ceros TCP and Jason group; 95% CI = 95% confidence interval; NB = new bone; MS = marrow space/soft tissue; MT = mineralized native tissue; RG = residual graft.

The histomorphometric analyses did not reveal significant differences, but the difference between groups involving residual graft approached significance. In particular, the percentage of residual graft using the marrow spaces and soft tissue as reference tended to be greater in the CJ group.

The two membranes are both porcine collagen membranes but with several differences. Microscopically, Jason membrane shows a multilayered structure with an interconnective pore system, whereas Bio-Gide shows a bilayered fibrous structure.[23] In vitro, Jason showed superior cell proliferation to that observed with Bio-Gide.[23] In a dog model, considerable biodegradation was noted within 4 to 8 weeks with Bio-Gide, whereas Jason membrane was resorbed generally within 8 to 12 weeks.[23]

In a comparative study investigating the augmentation of peri-implant dehiscence defects using different membranes in dogs, the final bone regeneration after 6 months was similar for all the membranes used.[6] Similarly, the present RCT found no remarkable differences in the results between the two membranes.

The two bone graft materials used in this study differ in that Bio-Oss is a xenograft derived from bovine bone without the organic substances, opportunely removed, whereas Ceros TCP is an alloplast, fully synthetic bone graft substitute made of pure beta-TCP.[24,25] Beta-TCP undergoes resorption via dissolution and fragmentation over a period of 6 to 18 months.[26] The complete resorbability of Bio-Oss is questionable. A 10-year case report study showed that resorption of the Bio-Oss is a slow but continuous process.[27]

In the present study, 6 months after the augmentation procedure, the Bio-Oss residual graft constituted 22% of the augmented tissue and new bone formation was 21%. Other studies reported residual graft of about 30% after 6 to 9 months of sinus augmentation.[28,29] The histomorphometric analysis in the Bio-Oss/Bio-Gide arm of an RCT on peri-implant horizontal defect showed residual graft of 28.9% after 6 months of follow-up.[16]

In the present study, the beta-TCP residual graft still constituted 28% of the augmented tissue, and new bone formation was 20%. Another study reported residual graft of 39% after 9 months of sinus augmentation.[29]

In a study on bone formation in rat calvaria defects, after 10 weeks, Bio-Oss had a greater percentage of bone formation compared with beta-TCP, which had greater percentage of bone formation compared with the control group.[26] This trend was also noted in a clinical study on sinus augmentation, in which a higher proportion of new vital bone was found in the Bio-Oss group compared with the beta-TCP group.[29] Differently, another study on dogs showed a greater bone area fraction for beta-TCP than for Bio-Oss at 24 months.[30] In addition, mean particle area fraction of beta-TCP decreased gradually until complete resorption occurred at 24 months, whereas Bio-Oss particles occupied a remarkable fraction of the area without significant resorption after 6 months.[30] In the present study, the follow-up period was 6 months, however the percentage of histomorphometric findings should change in time because of the faster resorption rate of beta-TCP.

In this study, the defects were filled with the bone substitute mixed with the autologous bone harvested during the implant insertion procedure. The autogenous bone could add the osteogenic and osteoinductive components that are necessary to achieve complete bone formation, even if the addition of 10% to 20% autogenous bone to the bone substitute did not significantly influence the new bone formation.[29]

A limitation of this histologic study was the small sample size, which led to low statistical power. In addition, an expert surgeon with more than 20 years of experience in implant surgery performed all the interventions. This should be taken into consideration when extrapolating the results from this trial to other settings.

In some cases, clinical measurements were not consistent with histologic findings. A clinical investigation with an appropriate sample size could verify these observations.

In conclusion, histomorphometric comparison between the two sets of combined biomaterials in a one-stage procedure for horizontal bone augmentation showed that the differences were not significant. Only the difference involving residual graft approached the level of statistical significance.

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