Original Research
Implantodontology

Split crest technique for implant treatment of agenesis of the upper lateral incisors: results of a randomized pilot histological and clinical study at 24-month follow-up

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Abstract: Agenesis of lateral incisors, besides the functional issues, represents a great esthetic drawback. The selection of an appropriate treatment is a complex decision, which should consider the stability of the clinical outcomes over time. The aim of the present study was a histological and clinical comparison of two-stage split crest technique (SCT), with bone chips alone or mixed with porcine bone in patients affected by unilateral and bilateral agenesis of the upper lateral incisors. Eleven patients were enrolled, and randomly assigned to receive a treatment with autologous bone chips (group 1) or autologous bone chips mixed 1:1 to porcine-derived xenogenic bone (group 2). After a 2-month healing period, implants were placed and biopsies harvested for histomorphometrical evaluation. Clinical assessment, according to ICOI PISA health scale, and radiographic marginal bone loss evaluation at 12- and 24-month follow-ups were conducted. The histomorphometry showed significantly greater new bone formation ($p > 0.0229$) in group 2. At 12- and 24-month follow-ups, all the evaluated implants, regardless of the group they were allocated, could be categorized as "success" in the ICOI Pisa Health Scale for Dental Implants, and did not show significant difference in crestal bone loss. To the best of our knowledge, these are the first histological and clinical outcomes indicating that the use of bone chips mixed 1:1 to porcine bone in SCT could be a promising technique for the rehabilitation of patients with agenesis of the upper lateral incisors, although studies with a larger number of patients and implants, and a longer follow up are needed.

Keywords: Bone Regeneration; Bone Substitutes; Guided Tissue Regeneration.

Introduction

Missing teeth can result from trauma, caries, periodontal disease and other infections, or dental agenesis.[1] Tooth agenesis accounts for between 2 and 10% of missing teeth;[2] specifically, lateral incisors represent the second most commonly affected teeth, excluding third molars and second premolar.[3] Congenitally missing lateral incisors are more frequent

bilaterally than unilaterally,[4] and they are reported slightly more in women than in men.[5] Agenesis of the lateral incisors, besides the functional issues, is a great esthetic inconvenience. Indeed, selecting the appropriate treatment approach is a complex decision, which depends on the patient's existing malocclusion, growth pattern, profile, smile line, size, shape, and color of the teeth, and amount of residual bone,[6] but, most importantly, the treatment selected has to guarantee functionally, esthetically, and periodontally acceptable results that remain stable over the long term.

The main advantage of orthodontic gap closure is that this approach preserves the natural architecture of the hard and soft tissues, although canines and premolars sizes and shapes should be adjusted to mimic the replaced teeth, eventually resorting to odontoplasty or veneers.[7] The alternative is the replacement by dental implants, which may represent a suitable solution as it can lead to predictable results.[8] However, it is a technique- and operator-sensitive procedure,[9] and complications may occur, such as marginal bone loss, gingival recession, and incomplete papilla filling. In patients with long-standing edentulous arches where bone resorptions (both vertically or horizontally) or combined bone defects are frequently present, the implant-prosthetic rehabilitation should be carefully approached because in those cases augmentation of the local bone volume is often necessary and therefore there is a need for additional techniques, which make the rehabilitation more challenging and less predictable.

In order to achieve an adequate treatment outcome from functional and esthetic points of view,[10,11] and to obtain a correct prosthetic rehabilitation,[12] it is important to have at least 1 mm of width around the implant bone crest at the buccal and palatal planes. Intra-oral tissues (mandibular branch) or extra-oral tissues (*e.g.*, iliac crest bone) grafts usually lead to good results, but they need invasive procedures and complications can occur, such as additional surgical procedures.[13] As an alternative solution in such cases, techniques for crest expansion using bone expanders or osteotomes, or "split-crest" (SCT) performed with an ultrasound device or with conventional surgery have been proposed.[14,15,16] The "split-crest" technique consists of splitting the buccal and palatal cortical plates,[17] displacing the vestibular cortical bone, both in maxilla or mandible, separating them from the bone marrow, and creating a middle gap, which is usually occupied by the inserted implants. The space unoccupied by the implants can be filled with biomaterials such as autologous bone grafts, particulate bone, or plasma derivatives as platelet-rich plasma.[18,19]

The present study aimed at histologically and clinically comparing two-stage SCT with bone chips alone vs bone chips mixed 1:1 to porcine bone in patients affected by unilateral and bilateral agenesis of the upper lateral incisors. The hypothesis of the study was that at 2 months the performance of the autologous bone chips is better than autologous bone chips mixed with porcine-derived xenogenic bone, with greater new bone formation and fewer residual biomaterial, and that the implants inserted in the sites regenerated with autologous tissue show a greater success rate.

Methodology

Patients' enrollment

The present study was conducted at the Orthodontic Unit of the Department of Oral and Maxillo-Facial Sciences of "Sapienza" University of Rome, Italy, between January 2016 and January 2019. It was designed as a prospective, randomized controlled single-center pilot study (in order to have data to run a power analysis for the sample size calculation). Eleven patients (7 females and 4 males, age range 19–22, mean age 20.45) with unilateral or bilateral agenesis of the upper lateral incisors were recruited.

The following criteria were used for patient's eligibility: a) a minimal horizontal bone width of 2 mm; b) a minimal vertical bone height of 10 mm; and c) no concavity in alveolar bone profile. Exclusion criteria were as follows: a) presence of systemic disease, b) alcohol or drug abuse, c) heavy smoking (more than 10 cigarettes/day), d) presence of oral tumors and/or ulcers, e) presence of infection and/or tooth remnants, f) poor oral hygiene, g) presence of parafunctional habits (clenching and/or bruxing), and h) psychiatric diseases.

All treated patients underwent orthodontic treatment in order to regain space for the subsequent implant-prosthetic rehabilitation. At the end of the orthodontic treatment, not all patients had 1st class occlusal relationships. Nevertheless, they were provisionally rehabilitated with an adhesive bridge (Maryland bridge), and once the skeletal maturity was achieved — in order to avoid further radiological examinations, the age of 19 was considered a threshold value[20] — they underwent implant rehabilitation. All patients were informed of the study protocol, of the therapeutic alternatives, and of the possible complications, and they all signed an informed written consent. The study protocol was evaluated and approved by the Ethical Committee of "Sapienza" University, Rome (# 4871), Italy, and was carried out in accordance with the fifth revision of the World Medical Association Declaration of 2000. The surgical interventions were performed by the same clinician (MC), specialized in implant dentistry. The Consort checklist was followed for this study. Randomization was performed prior to surgery by opening a sequentially numbered sealed envelope corresponding to the patient recruitment number. The randomization sequence was created using CLINSTAT (Martin Bland, York, United Kingdom) statistical software. The eligible patients were randomly assigned to receive a treatment with autologous bone chips (Group 1) or with autologous bone chips mixed 1:1 to porcine-derived xenogenic bone (Group 2). The assignment was concealed from the clinician until the beginning of implant surgery. All study operators were aware of the allocation of patients.

Surgical procedure

The surgical sites were assessed by clinical intraoral examination and panoramic and periapical radiographs. The two-dimensional radiographs (panoramic and periapical) were used to determine the height of the alveolar bone and the root inclination of the adjacent teeth. A caliper (Weiss modified Castroviejo curved calipers, Hu-Friedy, Chicago, USA) was used to determine the thickness and profile of the ridge. When the clinical examination raised diagnostic doubts about the presence of an alveolar width of at least 2 mm and the presence of a concavity, a computed tomography (CT) was requested for a 3D pre-operative evaluation. The CT images, in DICOM format, were imported in a software (SimPlant, Materialise, Leuven, Belgium) and the measuring tool was used for the evaluations.

Antimicrobial prophylaxis was obtained with 2 g amoxicillin 1 hour before surgery. Patients' mouths were rinsed with a chlorhexidine digluconate 0.2% solution for 2 minutes. After local anesthesia (Optocain®, Molteni Dental, Italia), a full thickness crestal incision extended buccally and palatally was made with vertical divergent releasing incisions extended into the vestibule. A mucoperiosteal flap was elevated palatally and buccally, and the bone ridge was exposed. The cortical bone was initially curetted to remove all residual connective tissue and periosteum, then, using a piezoelectric scalpel a horizontal incision was made in the middle of the ridge with two releasing incisions, one mesial and one distal. The horizontal osteotomies were performed at a distance of at least 1 mm from the neighboring teeth.[21] The alveolar ridge was split longitudinally in two parts, provoking a greenstick fracture using a 4 mm straight osteotome (Hu-Friedy Mfg. Co., Chicago, USA), used for cutting or preparing bone with depth markings. The straight osteotome was gently tapped on with a hammer to create a fine cut longitudinal to the crest. The osteotome was then used as a lever to spread apart the two cortical plates. Considering the importance of primary implant stability, the implant apex was positioned in the native bone for at least 2–3 mm. Accordingly, the surgical fracture was extended to a variable depth of 7 to 10 mm. Many attempts were made to avoid sharp and complete vertical or horizontal fractures of the buccal and palatal bone plates. After a crestal incision, bone from the retromolar trigone was harvested using a trephine (4 x 6 mm) and then fragmented into particles (bone chips) with a bone mill (R. Quètin, Leimen, Germany). The patients were then divided into two groups: Group 1 (5 patients: 5 female): the bone defect obtained by the separation of the bone segments was filled with bone chips, which were condensed in the space between the buccal and palatal bone plates with the aim of completely filling the space;

Group 2 (6 patients: 2 females and 4 males): bone chips were mixed with a bone substitute of porcine origin in a 1:1 ratio (OsteoBiol® granules, Gen-Os®, Tecnoss, Giaveno, Italy). The bone was covered with a titanium mesh 0.1 mm thick (Omnia, Fidenza, Parma, Italia), shaped, adapted, and fixed to contain the grafted material and avoid dispersion. Titanium microscrews Ø 1.5 mm (Omnia, Fidenza) were used to stabilize the mesh. The mesh was appropriately contoured to extend 3 to 4 mm over the bone margins of the defects. The mucoperiosteal flap was sutured using tension-free single sutures (GORE–TEX, W.L. Gore & Associates, Inc., Flagstaff, USA). Postsurgical analgesic treatment was administered with 100 mg nimesulide twice daily for 3 days; 1 g amoxicillin was prescribed twice a day for 5 days and the patients were instructed to use 0.12% chlorhexidine digluconate solution twice daily for 1 minute for oral hygiene maintenance. Suture removal was performed 10 days after the surgical procedure.

After a period of 2 months, the mesh was removed to insert the implants (UF II Implant System-DIO Implant, Busan, Republic of Korea), (9 implants in group 1 and 7 implants in group 2) of at least 3.8 mm in diameter and 10 mm in length. A total of 16 bone cores, 9 in group 1 (4 in 1.2 and 5 in 2.2 regions) and 7 in group 2 (4 in 1.2 and 3 in 2.2 regions) one for each implant inserted, were harvested using a 3.5 × 10 mm diameter trephine bur under saline solution irrigation and processed.

The retrieved specimens were immediately stored in 10% buffered formalin and processed to obtain thin ground sections with the Precise 1 Automated System (Assing, Rome, Italy).[22] They were dehydrated in ascending series of alcohol rinses and embedded in a glycolmethacrylate resin (Technovit 7200, VLC, Kulzer, Wehrheim, Germany). After polymerization, the specimens were sectioned along their longitudinal axis with a high-precision diamond disc at about 150 microns and ground down to about 30 microns. Then, the slices were stained with acid fuchsin and toluidine blue. A researcher (C.D'A.), not involved in patient selection and surgical procedures, performed the histological observations and histomorphometric analysis. Specifically, histomorphometry of the percentage of newly formed bone, marrow spaces, and residual biomaterial was carried out (primary outcome) using a light microscope (Leitz Laborlux, Wetzlar, Germany) connected to a high resolution video camera (3CCD, JVC KY-F55B, JVC, Yokohama, Japan) and interfaced to a monitor and PC (Intel Pentium III 1200 MMX, Intel, Santa Clara, USA). This optical system was associated with a digitizing pad (Matrix Vision GmbH, Oppenweiler, Germany) and a histometry software package with image capturing capabilities (Image-Pro Plus, Media Cybernetics Inc., Immagini e Computer Snc, Milano, Italy).

Two months after the implant insertion, at the second stage surgery, all implants were loaded with a provisional cemented acrylic resin crown and, after further 6 months, a fixed permanent metal-ceramic prosthesis was delivered. The implants were clinically and radiographically evaluated at the time of insertion, and at 12 and 24 months follow-up according to ICOI PISA health scale[23] (secondary outcomes) (Figure 1). Specifically, marginal bone loss was evaluated on standardized periapical digital radiographs (DenOptix QST Digital X-ray Phosphor Plate System; Gendex Dental Systems, Lake Zurich, USA), as described in previous studies,[24,25] obtained at 0 month (implant insertion), 12 and 24 months, using the long cone paralleling technique. To reduce the symmetric imaging error in the vertical plane, the measurements in the computer software were calibrated using an implant of known length. The linear measurements were obtained using VixWin PRO dental imaging software (Gendex Dental Systems, Lake Zurich, USA). The coronal surface of the implant was taken as the reference line from which 2 perpendicular lines were dropped on the mesial and distal aspects of the implants to the first bone-to-implant contact. Comparative measurements of mesial and distal crestal bone levels adjacent to implants were made to the nearest 0.1 mm. A minimum of 3 readings were made for each case and the average values were used to calculate the amount of crestal bone loss. Subtracting the bone level at 0 month from the bone level at 12 and 24 months gave the bone loss. A researcher (F.A.) not involved in patient selection and surgical procedures performed the radiographic measurements.

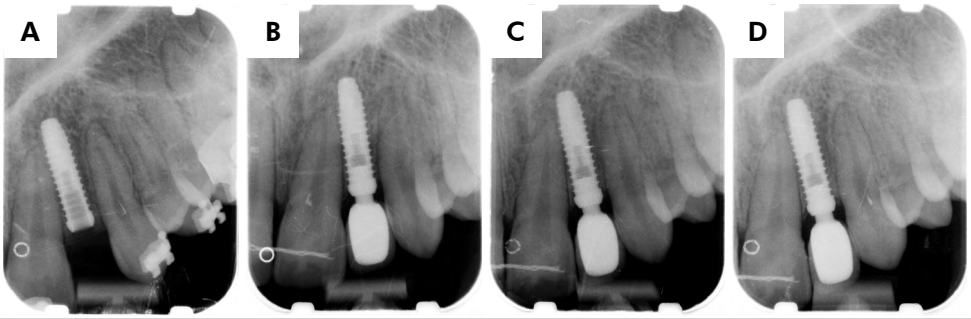

Figure 1. Group 2: (A) radiographic control after implant placement, (B) radiographic control at the fixed permanent prosthesis delivery, (C) radiographic control at 12 months after implant placement, and (D) radiographic control at 24-month after implant placement.

Statistical analysis

Radiographic data on the marginal bone loss and histomorphometric data on the percentages of new bone, residual biomaterials, and marrow spaces were subjected to statistical analysis using Kruskall-Wallis. All the data are presented as mean ± standard deviation (SD); statistically significant differences were accepted as $p < 0.05$.

Results

Histological results

Group 1

At low power magnification, some specimens appeared to be constituted by two areas with different features: the first one characterized by pre-existing bone with small remodeling areas and the second one where some residual autologous bone particles and new bone formation (Figure 2A); these two portions were clearly marked by a thin layer of necrotic bone probably due to the surgical trauma and acting as a structural support during the initial healing phase, and being replaced by vital bone during the remodeling stage (Figure 2B).

Only areas of regenerated bone with new bone trabeculae and residual autologous bone particles composed the remaining specimens. At high power magnification, in all the portions where regenerated bone was evident, the biomaterial particles were completely osseointegrated and showed irregular margins, typical of a previous resorption process. The newly formed bone in contact with the biomaterial particles showed wide osteocyte lacunae, typical of newly-formed bone. In the marrow spaces, close to the newly formed bone, many blood vessels were observed. Inflammation and multinucleated giant cells were absent (Figure 3). Histomorphometric analysis showed that the percentage of newly formed bone was 17.06 ± 2.91%, marrow spaces 60.08 ± 1.8% and residual grafted material 22.84 ± 1.95%.

Group 2

At low power magnification, newly formed bone with marrow spaces and residual biomaterials particles were observed (Figure 4A). In the marginal portion of some samples, pre-existing bone with small remodeling areas could be observed (Figure 4B). Residual autologous bone particles showed different sizes, the bigger ones measuring about 1000 microns and appearing paler than the small ones that were more intensely stained as surrounded by recently remodeled bone. The porcine-derived xenogenic bone particles were located among the autologous bone chips and all of them were completely or partially lined by new bone; in many fields their contact was very tight and ongoing bone formation was proved by osteoblasts that were in the process of depositing osteoid matrix directly on the particle surface (Figure 5). In many areas, collagen matrix undergoing remodeling process was present. In the marrow spaces there were some blood vessels close to the newly formed bone and the biomaterial particles (Figure 6). In a field, a multinucleated giant cell, located in a resorption lacuna, could be observed on the biomaterial surface. Histomorphometry showed that newly formed bone represented 22.1 ± 4.81%, marrow spaces 51.8 ± 3.65%, and the residual graft material

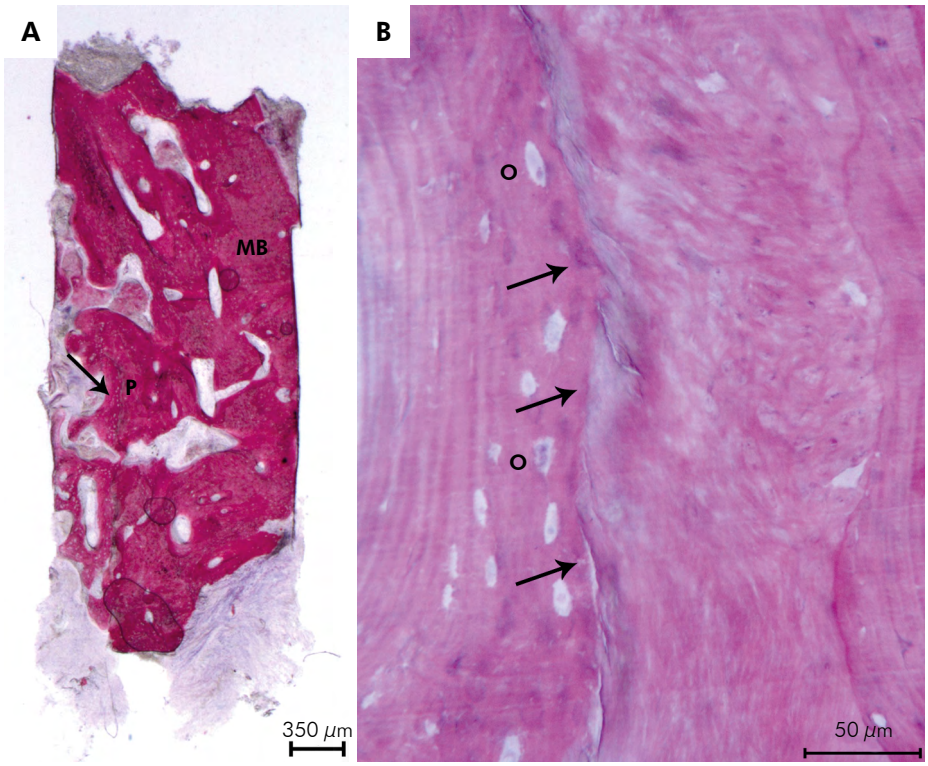

Figure 2. Low power magnification image of Group 1 sample (bone chips). (A) It was possible to distinguish two areas with different features: pre-existing bone with small marrow spaces (*) (MB) and new bone (black arrow) surrounding bone chips (**) (P) (Toluidine blue and acid fuchsin 12x); (B) A thin layer of necrotic bone (arrows) marked out the two areas: on the right-hand side remodeling areas could be observed, whilst on the left-hand side wide osteocyte lacunae (O), typical of young bone, were present. (Toluidine blue and acid fuchsin, 200 x).

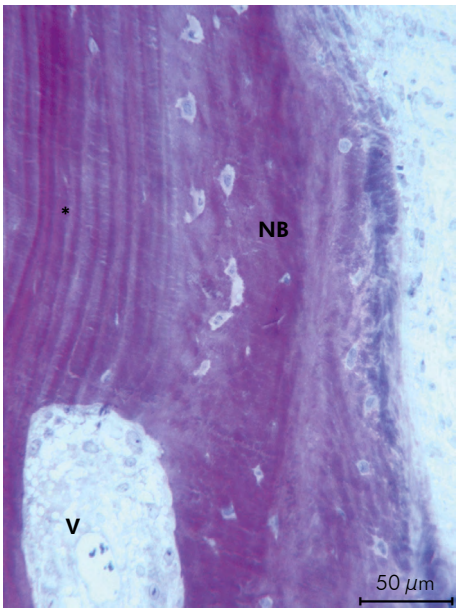

Figure 3. Group 1: inflammation and multinucleated giant cells were absent around the newly formed bone (NB) surrounding autologous bone particles (*). Blood vessels (v) were evident in the marrow spaces. (Toluidine blue and acid fuchsin, 200 x).

26.1 ± 3.51%. Statistical analysis revealed significant differences between the two groups in all the evaluated parameters (Table 1). The histomorphometry showed a significantly greater new bone formation ($p < 0.022$) and residual biomaterial percentages ($p < 0.030$) in Group 2, while marrow spaces were significantly less ($p < 0.002$).

Clinical results

No dropout at the end of the follow up period was observed. Clinically, 24-month after implant surgery, progress was uneventful for all the implants. Indeed, according to the ICOI Pisa Health Scale for Dental Implants, all the implants could be categorized as "success" because no pain, mobility, or exudates history was observed and the radiographic bone loss was < 2 mm in both test and control groups; therefore 100% early success rate was found over the whole follow-up (Figure 7). Remarkably, statistical

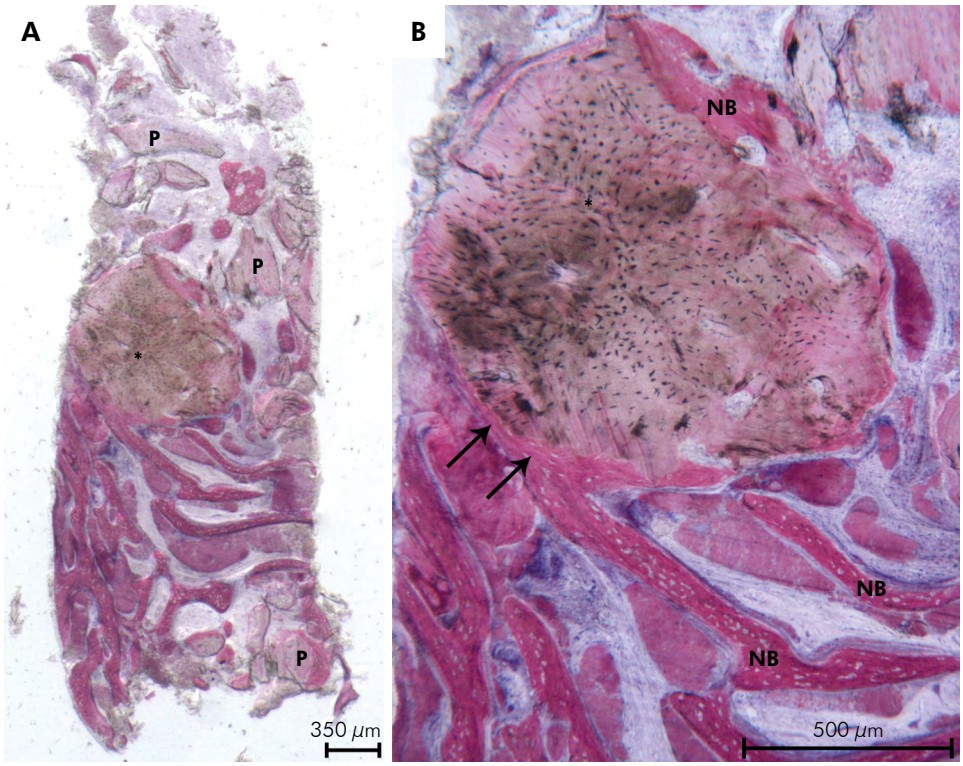

Figure 4. Low power magnification image of a Group 2 sample (autologous bone chips + porcine-derived xenogenic bone). (A) Newly formed trabecular bone with marrow spaces and residual bone chips (*) and porcine bone (P) particles were present (Toluidine blue and acid fuchsin, 12x); (B) an autologous bone particle (*) lined by newly formed bone (arrows) with wide osteocyte lacunae and areas of new bone formation (NB) could be seen. (Toluidine blue and acid fuchsin, 200 x).

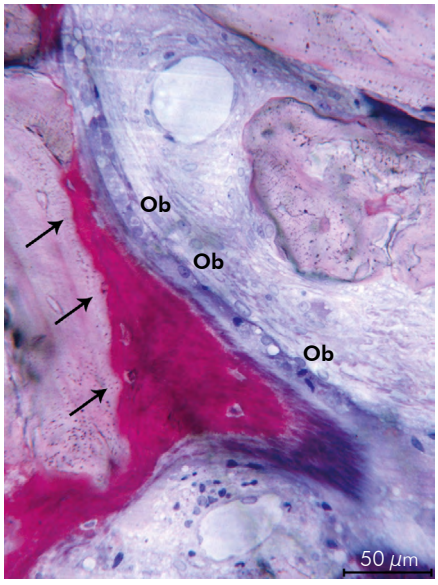

Figure 5. Group 2: in a marrow space a rim of osteoblasts (Ob) deposing new bone directly on the porcine bone granule surface was evident. The portion of the particle in contact with the young bone was intensely stained and showed irregular margins (arrows), so it might have previously undergone a resorption process (Toluidine blue and acid fuchsin, 200 x).

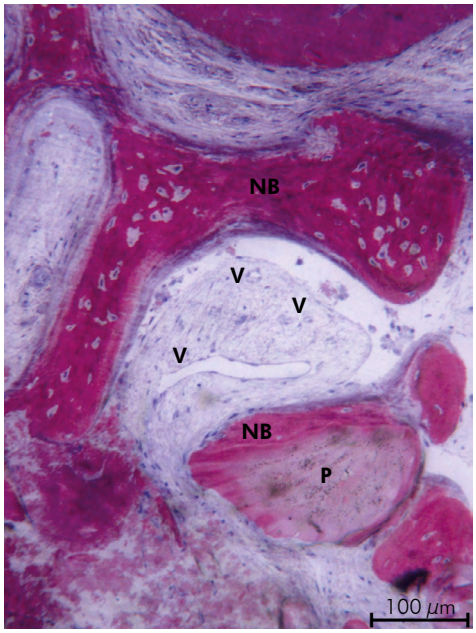

Figure 6. Group 2: in the marrow spaces some blood vessels (v) close to the newly formed bone (NB) and the biomaterial particles (P) undergoing remodeling could be observed. (Toluidine blue and acid fuchsin, 100 x).

Table 1. Statistical comparison of histomorphometric data in group 1 (n = 9 bone cores) and group 2 (n = 7 bone cores), 2 months after surgery.

	New bone (%)	Biomaterial (%)	Marrow spaces (%)
Group 1	17.06 ± 2.91	22.84 ± 1.95	60.08 ± 1.88
Group 2	22.10 ± 4.81	26.10 ± 3.51	51.80 ± 3.65
p-value	0.022*	0.030*	0.002*

*Statistically significant.

comparison of crestal bone loss at both time points revealed no significant difference between the groups: during the first 12 months, controls showed 0.33 ± 0.32 mm and test 0.27 ± 0.15 mm (p =0.503). At the 24-month follow up, the crestal bone loss was 0.72 ± 0.32 mm and 0.68 ± 0.22 mm (p = 0.967), with a decrease of 0.39 mm after the first year in control site and 0.41± 0.07 mm in tests. No significant difference was found by comparing data at the mesial (12-month: p = 0.264; 24-month: p = 0.830) and distal aspects in both groups (12-month: p = 0.595; 24-month: p = 0.999) (Table 2).

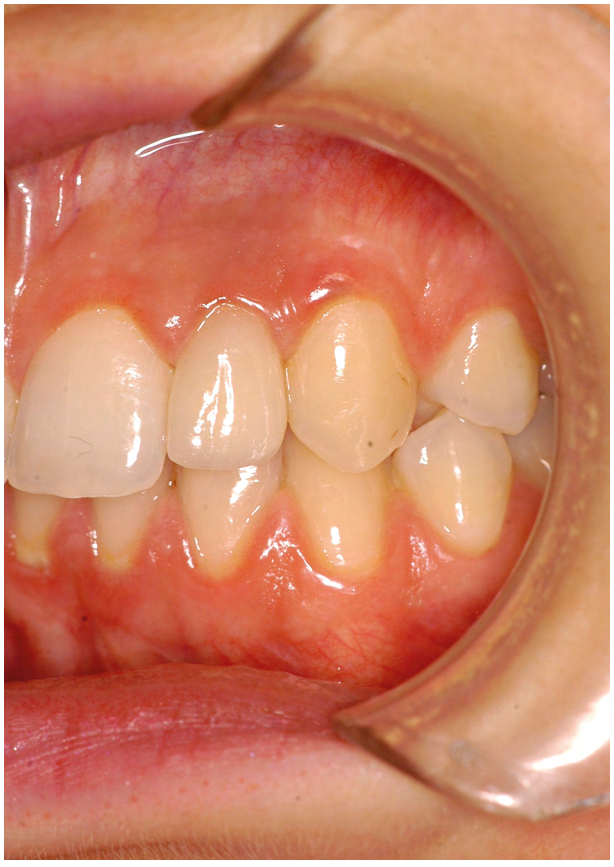

Figure 7. Clinical control at 24-month follow-up in a Group 2 patient.

Discussion

A conservative approach is usually advocated to minimize changes in the architecture of soft and hard tissues and to obtain a successful rehabilitation of young patients affected by agenesis of the upper lateral incisors. SCT has the advantage of a predictable expansion of the atrophic alveolar ridge,[26] especially when used to increase the width of the maxillary alveolar ridge.[27] In the present study, SCT was used as it shows a good buccal cortical bone preservation over time.[28] The bone loss around implants after separation of the cortical bone walls seems to be similar to that expected when implants are installed under ideal conditions.[29] This was a critical issue to be considered in the treatment plan as the implants were placed in young patients and in esthetic areas.

Moreover, in a recent review of the literature[26] aimed at determining the expected bone volume gain with the SCT, and how the use of surgical instruments affects the performance of this technique, it was concluded that the average bone gain in studies that used conventional surgical instruments was 3.61 mm, while this was 3.69 mm in those that used ultrasound, although no definitive recommendations can be made, due to the diversity of the studies, implant types, and implant design used. To the best of our knowledge, there is no conclusive evidence comparing traditional surgical instruments vs ultrasounds in term of crestal bone changes or implant survival/success, whilst there is agreement about the lower invasiveness and

Table 2. Bone loss pattern in group 1 (n = 9 implants) and group 2 (n = 7 implants). Implants from T0 (implant insertion).

Follow-up (months)	Group	n	Mean (mm)		Standard Deviation		p-value
			M	D	M	D	
12	1	9	0.41	0.26	0.31	0.34	0.503
	2	7	0.27	0.28	0.16	0.16	
24	1	9	0.77	0.66	0.35	0.29	0.967
	2	7	0.68	0.68	0.24	0.21	

M: mesial aspect; D: distal aspect; Group 1: control; Group 2: test; N: number of samples.

consequently patient discomfort[30,31] with the use of piezoelectric instruments. In the present study, a piezoelectric scalpel was used for the bone incisions due to its ease, safety, and precision in cutting hard tissues with a minor damage and moreover, because it could be handled in order to obtain curved cuts, which could help to shape the bone contour in esthetic areas. Indeed, no clinical complications were reported, and the healing was uneventful in the analyzed patients, supporting the general opinion of its safe use.

The application of bone substitutes into the gap between the bone plates is another critical issue, which needs further investigations. Histological studies could be relevant to deepen the understanding of bone biology following SCT and help make this technique even less invasive and safer, as their histomorphometric data can provide clinically relevant information on oral bone changes, especially in the lack of randomized controlled trials and metanalysis.[32] Ella et al.,[33] in a human study, compared SCT with and without a bone augmentation material and they found significantly less horizontal bone resorption in the grafted cases, whilst Tang et al.[34] found no difference between SCT in combination with a graft material when compared to SCT without it. In the present study, the patients were accurately selected according to the four requirements reported by Bassetti et al.[21] and Holtzclaw et al.[35] for the accomplishment of SCT and an histological and histomorphometric comparison of the early bone response to autologous bone alone or in combination with a biomaterial of porcine origin was performed. The percentages of new bone formation at 2 months were higher in the cases where the biomaterial was used, indicating that the intraoral harvesting of host bone could be reduced with less invasiveness for the patient and that a 2-month healing period can be recommended in such a clinical condition as all the implants placed in the present study resulted in Group I of PISA Health Scale for Dental Implants after a 24-month follow up, although this could be also due to the young age of the included patients. These results were also supported by a previous histological study on humans where porcine bone alone or in combination with autologous bone was evaluated in sinus augmentation procedures after only a 2-month healing period and the histomorphometric analysis revealed comparable percentages of newly formed bone, marrow spaces, and residual grafted material in both groups.[37]

Conclusion

To conclude, within the limits of the present study due to the relatively small number of enrolled patients, the clinical and histological outcomes indicated that the use of autologous bone chips mixed 1:1 to porcine-derived xenogenic bone in two-stage SCT could be a promising and effective technique, which enabled to achieve a functional and esthetic rehabilitation of patients with agenesis of the upper lateral incisors, after an accurate selection of the patients, the use of a piezoelectric device, the combination of SCT with bone augmentation materials, and the staged implant placement after a 2-month healing period. The hypothesis of the study was not confirmed. Indeed, the histomorphometric data about new bone formation percentages at 2 months showed significantly greater bone formation in the group with autologous bone mixed to porcine-derived xenogenic bone, and similar success implant rates at 12- and 24-month follow-ups.

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