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atrophic maxilla, bone augmentation, bone substitute, immediate loading, zygomatic implants

Randomised controlled trial

IMMEDIATELY LOADED ZYGOMATIC IMPLANTS *VERSUS* CONVENTIONAL DENTAL IMPLANTS IN AUGMENTED ATROPHIC MAXILLAE: THREE-YEAR POST-LOADING RESULTS FROM A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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PURPOSE. To compare the clinical outcomes of immediately loaded cross-arch maxillary prostheses supported by zygomatic implants *versus* conventional implants placed in augmented bone.

MATERIALS AND METHODS. Seventy-one edentulous patients with severely atrophic maxillae not having sufficient bone volumes for placing dental implants, or when it was possible to place only two implants of minimal diameter 3.5 mm and length of 8 mm in the frontal area and there was less than 4 mm of bone height subantrally were randomised according to a parallel-group design to receive either zygomatic implants (35 patients) to be loaded immediately or xenograft followed, after 6 months of graft consolidation, by placement of six to eight conventional dental implants submerged for 4 months (36 patients).
Outcome measures were: prosthesis, implant and augmentation failures, any complications, quality of life (OHIP-14), number of days with totally or partially impaired activity, time to function, and number of dental visits, as assessed by independent assessors.
Patients were followed up to 3 years after loading.

RESULTS. Eight patients from the augmentation group dropped out *versus* three from the zygomatic group. One augmentation procedure failed. Eight prostheses could not be fitted or failed in the augmentation group *versus* two prostheses in the zygomatic group, the difference being not statistically significant (difference in proportions = 18.18%; 95% CI: 1.44 to 34.91; P = 0.082). Nine patients in the augmentation group lost 42 implants *versus* three patients who lost six zygomatic implants, the difference being not statistically significant (difference in proportions = 21.65%; 95% CI: 2.02 to 41.20; P = 0.052). Sixteen augmented patients were affected by 30 complications *versus* 29 zygomatic patients (55 complications), the difference being statistically significant (difference in proportions = -30.87 %; 95% CI: -51.88 to -9.86; P = 0.007).
The 3-year OHIP-14 score was 4.11±7.27 in augmented patients and 4.51±6.23 in zygomatic patients, with no statistically significant differences between groups (mean difference = 0.40; 95% CI: -2.80 to 3.61; P = 0.624). Both groups had significantly improved OHIP-14 scores from before rehabilitation (P < 0.01 for both augmentation and zygomatic patients). Days of total infirmity were, on average, 7.42±3.17 in the augmentation group and 7.17±1.96 in the zygomatic group, the difference not being statistically significant (mean difference = -0.25; 95% CI: -1.52 to 1.02; P = 0.692). Days of partial infirmity were on average, 14.24±4.64 in the augmented group and 12.17±3.82 in the zygomatic group, the difference being statistically significant (mean difference = -2.07; 95% CI: -4.12 to -0.02; P = 0.048).
The mean number of days to functional prosthesis fitting were 444.32±207.86 in augmentation patients and 1.34±2.27 in zygomatic patients, the difference being statistically significant (mean difference = -442.98; 95% CI: -513.10 to -372.86; P < 0.001). The average number of dental appointments was 23.00±11.80 for augmentation patients and 20.05±6.23 for zygomatic patients, the difference not being statistically significant (mean difference = -2.94; 95% CI: -7.62 to 1.74; P = 0.213).

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CONCLUSIONS. On the one hand, three-year post-loading data suggest that immediately loaded zygomatic implants are associated with fewer prosthesis failures (two *versus* eight patients), implant failures (three patients lost 6 zygomatic implants *versus* nine augmentation patients who lost 42 implants) and less time needed for functional loading (1.3 days *versus* 444.3 days) as compared to augmentation procedures and conventionally loaded dental implants.
On the other hand, significantly more complications were reported for zygomatic implants; since there was an apparent increase in severe sinusitis at zygomatic implants over time, long-term data are required; however, in the short-term, zygomatic implants proved to be a better rehabilitation strategy for severely atrophic maxillae.

CONFLICT OF INTEREST STATEMENT. This study was originally supported by Nobel Biocare (Göteborg, Sweden), the manufacturer of the implants and provisional and definitive prosthetic components used in this study, which were provided free of charge to the patients; however, before any results were available, Nobel Biocare withdrew their financial support and further recruitment had to be stopped. Tecnoss (Giaveno, Italy) kindly donated the bone substitutes and membranes, whereas Global D (Brignais, France) donated the osteosynthesis screws. Data was entirely the property of the authors and by no means did the manufacturers interfere with the collection, analysis or publication of the results.

INTRODUCTION

Dental implants are used to replace missing teeth[1], but can be limited by insufficient bone volumes to allow their anchorage. In order to solve this problem, several bone augmentation procedures have been developed. In principle, the missing bone is taken from a donor site (for example the iliac crest), transplanted where needed, left to consolidate for several months, and then implants are placed. However, major bone grafting operations sometimes have to be undertaken under general anaesthesia, requiring patients to be hospitalised for a few days. Furthermore, two to three surgical interventions may be needed before the implants can be functionally used, with some patients having to wait more than 1 year before a prosthesis can be fixed to the implants. Moreover, the total cost of the treatment is high, and some degree of morbidity related to the donor site must be expected, although more recently bone substitutes are used to minimize morbidity[2-4].
As an alternative to bone augmentation procedures, a long, screw-shaped implant – the zygomatic implant – was developed by Professor P-I Brånemark at the beginning of the 1990s[5]. Initially, zygomatic implants were generally inserted through the alveolar crest and maxillary sinuses to engage the body of the zygomatic bone[6]. More recently, however, depending on the individual local anatomical conditions[7], they may be positioned external to the alveolar crest, engaging the maxillary sinus at a higher location. One to three zygomatic implants can be inserted through the alveolar crest to engage the body of each zygomatic bone, but more commonly two zygomatic implants are placed in each zygoma, and can be loaded immediately if inserted with sufficient torque[8]. This is a major potential advantage over conventional bone augmentation procedures, since patients can be functionally rehabilitated in a single day instead of undergoing two to three surgical procedures over the course of several months[3,9]. Zygomatic implants are therefore an alternative to conventional bone augmentation and implant rehabilitation for severely atrophic maxillae[6].
That being said, reliable comparative trials evaluating their effectiveness and potential risks

in comparison to conventional augmentation procedures are still lacking, despite the fact that zygomatic implants have been in use for more than 20 years[5,6,10-13]. In fact, the only randomised controlled trial (RCT) published on zygomatic implants to date was a split-mouth study comparing drilling *versus* piezo-surgery for zygomatic implant site preparation[9,14].

The aim of this RCT of parallel-group design was to compare the clinical outcomes of immediately loaded cross-arch maxillary prostheses supported by zygomatic implants *versus* conventional implants placed in augmented bone for the rehabilitation of patients with atrophic or severely atrophic maxillae. We plan to report data up to 15 years after loading, and this is the third of the planned publications. Data at 4 months[15] and 1 year[16] post-loading have previously been reported. This article is reported according the CONSORT statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/).

MATERIALS AND METHODS

Trial design

This was a three-centre RCT of parallel-group design with two arms, balanced randomisation, and blind outcome assessment when possible. Patients with totally edentulous atrophic maxillae were randomly allocated to bone augmentation with a bone substitute and six to eight conventionally loaded dental implants (augmentation group) or either four zygomatic implants or two zygomatic and two conventional implants to be immediately loaded (zygomatic group). Originally, another two centres agreed to participate in this trial and should have treated 20 patients each, but never provided any data.

Eligibility criteria for participants

Any patient with a severely atrophic edentulous maxilla not having sufficient bone volumes for placing any dental implants, or when it was possible to place only two implants in the frontal area (minimal diameter 3.5 mm and length 8 mm), and having a residual bone height under the maxillary sinus of less than 4 mm, as measured on conventional (CT) or cone-beam computer tomography (CBCT) scans, requesting a fixed prosthesis, and of age 18 or older and able to understand and sign an informed consent form was eligible for inclusion in this trial. Coronal slices were added to conventional CBCT/CT scans to evaluate the osteomeatal complex and the sinus epithelium conditions. Only patients with healthy sinuses were asked to join the trial.

Patients were not admitted to the study if any of the following exclusion criteria applied:

- General contraindications to implant surgery;
- Irradiation to the head and neck region with more than 70 Gray;
- Immunosuppression or immunocompromised;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Untreated periodontal disease;
- Poor oral hygiene and motivation;
- Uncontrolled diabetes;
- Pregnancy or lactation;
- Addiction to alcohol or drugs;
- Psychiatric problems;
- Lack of opposite occluding dentition/prosthesis;
- Restricted mouth opening (less than 3.5 cm inter-arch anteriorly);
- Acute or chronic infection/inflammation in the area intended for implant placement;
- Unable to commit to 15-year follow-up;

- Participation in other studies if precluding adherence to the present protocol;
- Referral for implant placement alone.

Patients were categorised according to the degree of the maxillary atrophy into: i) atrophic, if there was sufficient bone to place at least two 8-mm long and 3.5-mm wide implants in the frontal portion of the maxilla, and ii) severely atrophic if there was insufficient bone to place at least two 8-mm long and 3.5-mm wide implants in the frontal portion of the maxilla. Patients were also categorised into three groups according to their declarations: i) non-smokers, ii) moderate smokers (up to 10 cigarettes per day), and iii) heavy smokers (more than 10 cigarettes per day).

After informed consent was signed, patients were randomly allocated to either the zygomatic implant group (to be immediately loaded, either four zygomatic implants (**FIG. 1**) or two zygomatic and two conventional implants (**FIG. 2**) depending on the degree of jaw atrophy), or the bone augmentation group (depending on the degree of jaw atrophy, either bilateral sinus lift and horizontal augmentation with bone substitute **(FIG. 3**) or bilateral sinus lift only) followed by delayed placement of six to eight conventional implants to be loaded after 4 months of unloaded healing, according to the indications contained in the sequentially numbered envelope corresponding to the recruitment number of the patient.

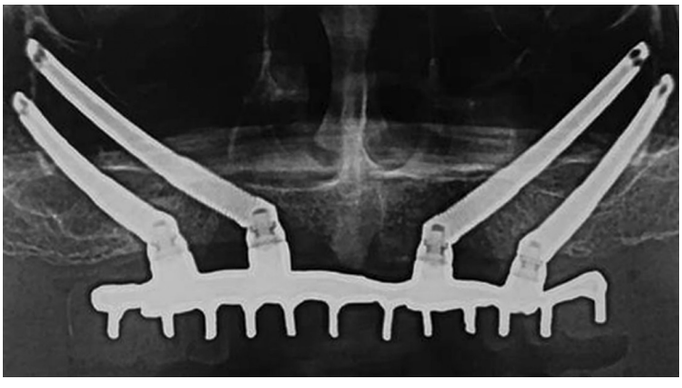

FIG. 1: *Panoramic radiograph at 3 years after loading in one of the patients with a severely atrophic maxilla randomly allocated to receive four immediately loaded zygomatic implants (Dr. Pistilli, Rome).*

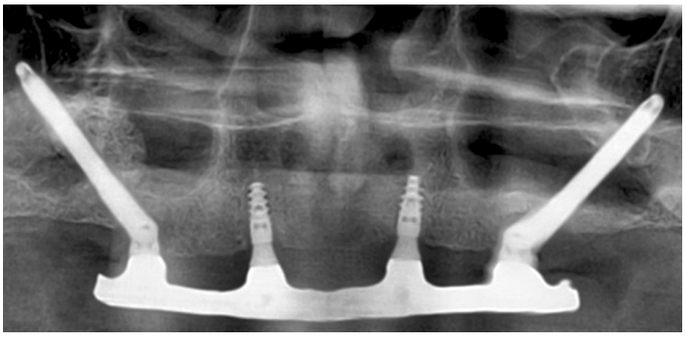

FIG. 2: *Panoramic radiograph at 3 years after loading of one of the patients with an atrophic maxilla randomly allocated to receive two immediately loaded zygomatic and two conventional implants (Dr. Felice, Rome).*

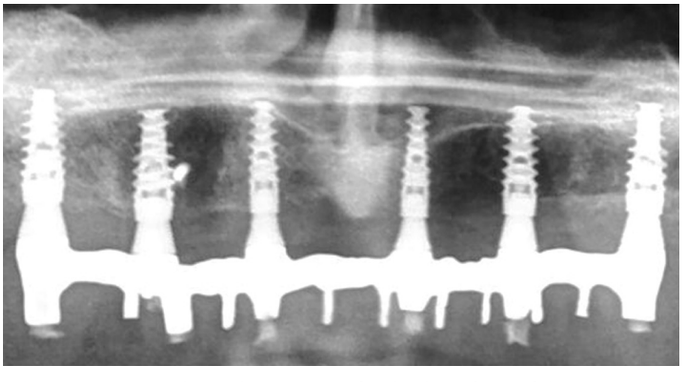

FIG. 3: *Panoramic radiograph at 3 years after loading of one of the patients with a severely atrophic maxilla randomly allocated to receive six to eight conventionally loaded implants after augmentation with bone substitutes (Dr. Pistilli, Rome).*

Setting and locations

Patients were treated at three different centres: i) the Hospital Clinic in Barcelona, Spain (which recruited 27 out of 40 planned patients, hereinafter referred to as Spain centre); ii) Sant'Orsola Malpighi Polyclinic in Bologna (10 out of 20 planned patients, Bologna centre) and San Filippo Neri Hospital in Roma, Italy (34 out of 30 planned patients, Rome centre).

The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to. The study was approved by the respective ethics committees of the Hospital Clinic in Barcelona (HCP/2011/063, 2 May 2011), the Sant'Orsola Malpighi hospital in Bologna (Prot. n 1633/2011, 19 July 2011), and the San Filippo Neri Hospital (prot. n. v.f. 03/2013 and prot n. 50/C.E.F.S.N., 27 May 2013). All patients received a thorough explanation, and signed an informed written consent form prior to being enrolled in the trial.

Surgical procedures

Stereolithographic models of the maxillae were created from CBCT/CT scans to best plan the implant insertion angles. The correct implant insertion axes were marked with a pencil. Diagnostic wax-up and surgical guides were prepared to help clinicians to select the most appropriate position and angulation of each implant. Efforts were made to plan implant exits at a crestal level rather than palatally.

Patients rinsed with 0.2% chlorhexidine mouthwash for one minute prior to any surgical procedure. Surgeons were free to decide with the patients the preferred type of anaesthesia (general anaesthesia with local anaesthesia, local anaesthesia with sedation, or local anaesthesia alone) to be administered. Articaine with epinephrine 1:100,000 was injected locally to reduce bleeding and increase visibility. Before augmentation and implantation procedures, systemic antibiotics (1750/250 mg of amoxicillin-clavulanic acid or 600 mg of clindamycin for patients allergic to penicillin) were administered orally, or, in the case of intravenous sedation/general anaesthesia (875/125 mg of amoxicillin-clavulanic acid or 300 mg of clindamycin for patients allergic to penicillin), intravenously prior to bone augmentation and implant installation.

Patients were randomised to two groups: zygomatic implants or bone augmentation; however, according to the degree of bone atrophy of the maxilla there were two different treatment alternatives in each group.

Zygomatic implants

1) *Four zygomatic implants in severely atrophic maxillae* **(FIG. 1).**

Quadruple zygomatic implants, two per side, were placed and immediately loaded (within 1 week) when they could be inserted with torque greater than 40 Ncm; otherwise, implants were submerged for 4 months. After crestal and release incisions, a mucoperiosteal flap was raised to expose the maxilla and enable identification of the infraorbital foramen and the notch between the zygomatic arch and the lateral and medial surfaces of the frontal process of the zygomatic bone. If necessary, a 10 x 5-mm or wider window extending from the sinus floor to the base of the zygomatic bone was opened on the lateral wall of the maxillary sinus, close to the infrazygomatic crest, and the sinus lining was carefully raised. When anatomical conditions allowed, zygomatic implants were not inserted through the alveolar crest into the sinus cavity but into or onto the bone external to the sinus, thereby involving only the upper portion of the sinus. Surgical templates were used to position the implant exit into the oral cavity at the crestal level and through the palate. A retractor was placed in the notch between the zygomatic arch and the lateral and medial surfaces of the frontal process of the zygomatic bone to facilitate proper three-dimensional orientation of the implant. While drilling,

adequate saline irrigation was provided; a round bur was used first, then a 2.9-mm diameter twist drill, until penetration of the outer cortical layer of the zygomatic bone was achieved at the notch. The length of the zygomatic implant to be used was determined with a straight depth indicator. A 3.5-mm diameter pilot drill was then used, followed by the 3.5-mm twist drill.

Brånemark System Zygoma Ti-Unite Implants RP (Nobel Biocare, Gothenburg, Sweden) having a diameter of 4 mm and the following lengths: 30, 35, 40, 42.5, 45, 47.5, 50 and 52.5 mm, were inserted, aiming to achieve an insertion torque of at least 40 Ncm to allow immediate loading. Bicortical engagement was always obtained, meaning that the tip of the implant protruded 1 to 2 mm on the other side of the zygoma. After the first implant was placed, the same procedures were repeated to place the second implant. We attempted to place the implant apices about 1 cm apart. Centres were allowed, at their discretion, to cover exposed implant threads using a paste made of 600–1000 micron pre-hydrated collagenated cortico-cancellous granules of porcine origin mixed with OsteoBiol Gel 0 in sterile syringe (OsteoBiol mp3, 1 cc, Tecnoss, Giaveno, Italy) and resorbable collagen barriers (OsteoBiol Evolution, Tecnoss). In alternative, the Bichat fat pads were exposed and gently shifted medially to cover the exposed implant portions (in 14 patients from the Italian centres). Flaps were then sutured with simple interrupted 4-0 resorbable sutures (Vicryl, Ethicon FS-2, Johnson & Johnson, New Brunswick, NJ, USA) around the impression copings.

2) *Two zygomatic and two conventional implants in atrophic maxillae* **(FIG. 2).**

One zygomatic and one conventional implant were placed per side, and immediately loaded (within 1 week) if an insertion torque of at least 40 Ncm had been achieved; otherwise they were submerged for 4 months.

The same procedure as described above was used to place the zygomatic implants. In addition, one conventional Nobel Active implant (Nobel Biocare) with internal connection was placed in the anterior zone (canine to canine) of each side, following the manufacturer's instructions and trying to achieve an insertion torque of greater than 40 Ncm to allow immediate loading. With respect to conventional implants, operators were free to choose implant lengths (8.5, 10, 11.5, 13 and 15 mm) and diameters (3.5, 4.3 and 5.0 mm) according to the clinical indications and their preferences. The following post-surgical instructions were given:

- 875/125 mg of amoxicillin-clavulanic acid, or 300 mg of clindamycin for patients allergic to penicillin, thrice a day for 1 week;
- Ibuprofen 600 mg to be taken 4 times a day during meals for 1 week, but patients were instructed not to take them in absence of pain;
- Xylometazoline hydrochloride (nasal decongestant) 1 mg, 5 drops thrice a day for 2 weeks;
- A soft diet for 2 weeks
- 0.2% chlorhexidine rinses twice a day for 2 weeks.

Patients were recalled and checked at day 3, day 10 (suture removal) and after 1 month.

Augmentation procedure and conventional implants

1) *Augmentation procedure and conventional implants in severely atrophic maxillae* **(FIG. 3).**

In the posterior maxilla, bilateral 2-stage sinus lift procedures were performed. After crestal and release incisions and mucoperiosteal flap elevation, a window was designed above the maxillary sinus floor using rotating burs or piezo-surgery. After internal displacement of the bony window, the maxillary epithelium lining was carefully raised, and the sinus was packed

with the mp3 bone substitute. In the event of rupture of the sinus lining, resorbable barriers (OsteoBiol Evolution) were used to contain the graft. In the anterior maxilla, collagenated blocks (OsteoBiol, Sp-Block) of equine cancellous bone were used as onlays/veneers. The blocks were hydrated with a sterile lukewarm physiological solution or antibiotics for 5 to 10 minutes before use.

Afterwards, they were modelled to be adapted to the receiving site, which was accurately decorticated to guarantee maximum contact and high blood perfusion. Blocks were fixed with osteosynthesis self-drilling Ti6Al4V microscrews (Graftek, Global D) of 1.5 or 2 mm diameter and various lengths, from 4 to 19 mm. mp3 bone substitute granules were used to fill the gaps between the recipient bone and the bone blocks. In alternative, small defects could be grafted with bone substitute granules alone, according to clinical indications and the surgeon's preference; nasal lift procedures using mp3 bone substitute granules could also be implemented. All the grafted areas and maxillary windows were covered with OsteoBiol Evolution resorbable barriers of equine pericardium. After 6 months healing, 6 to 8 conventional Nobel Active implants were placed and left to heal submerged for 4 months. Just prior to implant placement, a second CBCT scan was taken in order to properly evaluate bone anatomy and plan implant placement.

2) *Augmentation procedure and conventional implants in atrophic maxillae.*

Operators were free to choose 1- or 2-stage lateral window sinus lift procedures, as previously described, depending on whether the implants could be stabilised or not. In the case of a 1-stage sinus lift procedure, implants were left to heal submerged for 6 months. In the case of a 2-stage sinus lift procedure, 6 to 8 conventional Nobel Active implants were placed after 6 months of healing and then left to heal submerged for 4 months.

The same postoperative instructions as previously described were given, with the addition of the following:

- Avoid blowing the nose or using drinking straws;
- Keep the mouth open when sneezing in order to decrease intra-sinus pressure.

Patients with severely atrophic maxillae (subjected to horizontal augmentation procedures) were not allowed to wear any removable denture for at least one month postoperatively.

Prosthetic procedures

Prosthetic procedures at implants to be immediately loaded were initiated straight after flap suturing; similar procedures were implemented for implants in the augmentation group after their exposure. Panoramic radiographs were taken to verify proper seating of all the impression copings. A self-curing acrylic resin (DuraLay, Reliance Dental Manufacturing, Worth, IL, USA) was positioned on a brass wire to further stabilise the impression copings in position. A pick-up impression was taken using a polyether material (Impregum, 3M ESPE, St. Paul, MN, USA) and, when possible, using the patient's denture, with holes in the resin palate, as customised trays. Healing caps were positioned, and a screw-retained metal reinforced acrylic cross-arch provisional prosthesis was delivered within 1 week.

Three months after initial loading, the provisional prostheses were removed, implant stability was checked by tightening the abutment screws with 15 Ncm torque using a manual torque wrench, and definitive impressions were taken at abutment level using a rigid impression material and impression copings with an open tray as previously described. Within one month, definitive screw-retained cross-arch fixed Procera Implant Bridge Titanium (Nobel Biocare) with ceramic or acrylic veneer materials were to be fitted. However, due to misunderstanding of the financial agreements, 35 patients at the Italian centres did not receive the

definitive prosthesis 4 months after loading and the remaining patients did not receive Procera Implant Bridge Titanium prostheses.
Patients were enrolled in an oral hygiene programme with recall visits every 6 months. Operators were free to increase this frequency (every 2 to 4 months) based on individual needs. Dental occlusion was evaluated at each maintenance visit. Follow-ups were conducted by blind independent local outcome assessors.

Outcome measures

Outcome measures were the following.

- Prosthesis failure, defined as a prosthesis which could not to be fitted due to implant failure, or prosthesis replacement for any reason.
- Implant failure, defined as any implant displaying rotational mobility, any infection dictating implant removal, and/or any mechanical complication rendering the implant unusable (e.g., implant fracture or deformation of the connecting platform). Implant stability assessments were performed, with the prostheses removed, at abutment connection (augmented group only) and at delivery of the definitive prostheses or 4 months after loading and at 1 and 3 years after loading, by tightening the abutment screws with 15 Ncm torque. Rotating implants were considered failures and were removed. A few zygomatic implants displayed a slight horizontal mobility due to their lengths and the lack of alveolar bone at their exits; this was recorded, but the implants, if they did not rotate, were considered successful and left in place.
- Any biological or prosthetic complications.
- Failure of the augmentation procedure; the augmentation procedure was to be considered a failure if, after it had been performed, it was not possible to place the planned implants in the augmented site.
- Peri-implant marginal bone levels on periapical radiograph, to be reported at the end of the first and third year of post-loading follow-up; however the Spanish centre took only panoramic radiographs and the Italian centres did not take periapical radiographs as planned, since Dr. Felice and Dr. Pistilli only took periapical radiographs of 8 patients each at 1 year after loading. This outcome measure therefore had to be discontinued.
- Oral Health Impact Profile (OHIP-14), which measures people's perceptions of the social impact of oral disorders on their well-being[17]. There are 14 questions which can be answered in the following way: never = 0, hardly ever = 1, occasionally = 2, very often = 3, or fairly often = 4. The maximum possible score is 56, and corresponds to the most negative outcome. Scores were recorded at patient enrolment prior to any intervention, and 1–2 weeks after definitive prostheses delivery, or about 4 and a half months after initial loading, and at 1 and 3 years after loading. Patients with a complete treatment failure who were rehabilitated with alternative treatments other than the randomly allocated intervention they were supposed to have were not counted.
- Number of days with totally or partially impaired patient activity. Days of totally impaired activity were those days in which, in the patient's opinion, (s)he could not perform his/her ordinary life activity, including work. Days of partially impaired activity were those days in which, according to the patient, (s)he could only partially perform his/her ordinary life activity, including work. This should have been assessed at the fitting of the definitive prostheses, but was actually assessed at 3 months after loading.
- Time to function. Number of days from the first surgical intervention to the delivery of the implant-supported provisional prosthesis.

- Number of sessions with the dentist. Total number of appointments required by the patient over the entire follow-up period (up to 3 years post-loading), including regular check-ups and sessions for treatment of complications.

With respect to complications and graft, implant and prosthesis failures, we have only reported them when they occurred at the first original procedure. Those occurring to rescue implants/procedures were not reported, since they were beyond the scope of this trial.

Sample size, random sequence, allocation concealment and blinding

The sample size was calculated for the primary outcome measure (patient experiencing at least one implant failure): a two-group continuity corrected chi-squared test with a 0.050 two-sided significance level has 80% power to detect the difference between a proportion of 0.100 and a proportion of 0.300 for patients experiencing at least one implant failure (odd's ratio of 3.857) when the sample size in each group is 72. It was planned to recruit 65 patients per group over a 3-year recruitment interval period, since this was the maximum number that clinicians committed to treat, but only 35 and 36 patients per group could be actually recruited.

Five computer-generated restricted randomisation lists were created with equal numbers of patients in both groups. Only one of the investigators (Dr. Esposito), not involved in the selection and treatment of the patients, was aware of the randomisation sequence and could have access to the randomisation list, stored on his password-protected laptop computer. The randomisation codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially after patients were enrolled in the trial, and treatment allocation was therefore concealed to the investigators in charge of enrolling and treating the patients.

Outcome assessors (Dr. Ada Ferrer in Spain; Dr. Salvatore Di Simone at the Bologna centre and Dr. Roberto Cassoni at the Rome centre), not involved in the treatment of the patients, measured the following parameters at each centre: implant failures, quality of life (OHIP-14), number of days of totally or partially impaired patient activity, time to function, and number of sessions, which were assessed without knowing group allocation when possible. Complications were registered and treated by the treating dentists in a non-blinded mode.

Statistical methods

All data analysis was carried out according to a pre-established analysis plan. A dentist with expertise in statistics (Dr. Agnese Ferri) analysed the data without knowing the group codes. The patient was the statistical unit of the analyses. Differences in the proportions of prosthesis failures, implant failures, augmentation procedure failures and complications were compared between groups using Fisher's exact probability test. Differences between the groups in numbers of days with totally or partially impaired activity, time to function, and number of sessions with the dentists were compared via independent-samples t-tests. A Mann–Whitney U-test was used to compare the OHIP-14 scores between groups. Comparisons between the 3-year post-loading endpoints and the pre-operative measurements were made using Wilcoxon tests, to detect changes in OHIP-14 scores for each study group.

Comparisons among the three centres were carried out using a one-way ANOVA for continuous variables (difference in number of days with total or partial inactivity, time to function, and number of session with the dentists), a Pearson's chi-squared test for categorical data (difference in proportions of prosthetic, implant and augmentation procedure failures, drop-out and complications) and a Kruskal–Wallis test for ordinal variables (difference in OHIP-14 sco-

res). Finally, the post-hoc test used was an independent t-test with Bonferroni correction of the P-value (P = 0.017). All statistical analyses were conducted using Stata software (version 15.1, StataCorp LLC, College Station, Texas, USA). All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Ninety-three patients were screened for eligibility, but 22 patients were not enrolled in the trial: 16 patients did not want to participate in the trial for various reasons, three patients had more bone volumes than required by the inclusion criteria, two were under treatment with bisphosphonates, and one had just been diagnosed with breast cancer. Seventy-one patients were considered eligible and were consecutively enrolled and treated in the trial. All patients were treated according to the allocated interventions.

Eight patients from the augmentation group and three from the zygomatic group dropped out, specifically the following.

Augmentation group:

- Patient 5/Spain, died before the 4-month post-loading follow-up due to gastric cancer;
- Patient 8/Spain, died before the 4-month post-loading follow-up due to lung cancer;
- Patient 14/Rome, last seen at 4 months post-loading, then moved away; contacted by phone and reported being fine; OHIP-14 scores given by phone;
- Patient 19/Bologna, could not be contacted; last seen at 4 months post-loading;
- Patient 1/Bologna, could not be contacted; last seen at 1 year post-loading;
- Patient 9/Bologna, could not be contacted; last seen at 1 year post-loading;
- Patient 12/Bologna, last seen at 1 year post-loading, then moved away; contacted by phone and reported being fine; OHIP-14 scores given by phone;
- Patient 14/Bologna, last seen at 1 year and 8 months post-loading, then moved away; contacted by phone and reported being fine; OHIP-14 scores given by phone.

Zygomatic group:

- Patient 13/Bologna, could not be contacted; last seen at 1 year post-loading;
- Patient 8/Rome, moved abroad and unable to contact; last seen at 1 year and 4 months post-loading;
- Patient 23/Bologna, last seen at 1 year and 6 months post-loading, then moved away; contacted by phone and reported being fine; OHIP-14 scores given by phone.

The data pertaining to all remaining patients was evaluated in the statistical analyses, with the exception of the peri-implant bone level changes.

The following protocol deviations were observed:

- Thirty-five patients from the Italian centres and three from the Spanish centre did not receive the definitive prosthesis during the first 4 months in function;
- Nine patients who were rehabilitated with definitive prostheses in Bologna and Rome did not receive the planned Procera Implant Bridge Titanium prosthesis, but instead conventional screw-retained cast metal-acrylic, metal-ceramic cross-arch or carbon fibre-composite prostheses;
- Patients received different numbers than those attributed by the random list (Spanish centre only);
- The Spanish centre recruited and treated 27 instead of the 40 planned patients. Bologna recruited 24 instead of the 30 planned patients, but, due to organisational reasons only, the first 10 patients were treated in Bologna and the remaining 14 patients recru-

ited in Bologna centre were treated by the same dentist (Dr. Felice) in Rome. The Rome centre recruited all 20 patients as planned;

- One patient who should have received only two zygomatic implants (one per side) actually received one additional zygomatic implant, since the distance between the conventional implant in position 11 and the zygomatic one was considered to be too great by the surgeon (Dr. Pistilli);
- In one patient, absorbable gelatine haemostatic sponges (Spongostan Special, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA) were used to protect the sinus epithelium after its displacement;
- The Spanish centre took only panoramic radiographs and the Italian centres did not take periapical radiographs as planned for all patients since Dr. Felice and Dr. Pistilli only took periapical radiographs of 8 patients each at one year after loading and then discontinued this practice;
- One patient from the augmentation group postponed abutment connection by 28 months for personal reasons (Spanish centre).

Patients were initially treated from February 2012 to September 2015. The follow-up of all patients reported here is 3 years after prosthesis loading.

The main baseline patient characteristics are presented in **TABLE 1**. There were no apparent systematic baseline imbalances between the two groups.

An overall comparison of all outcome measures at 3 years post-loading is presented in **TABLE 2**.

- Graft failures. One patient from the augmentation group was last seen one month after the augmentation procedure. She reappeared after 3 years but the graft and the maxilla were totally resorbed so she was rehabilitated with zygomatic implants outside this trial.
- Prosthesis failures (**TABLES 3A, 3B**). Eight prostheses in the augmentation group could not be fitted or failed, *versus* two prostheses in the zygomatic group, the difference not being statistically significant (difference in proportions = 18.18%; 95% CI: 1.44 to 34.91; P = 0.082).
- Implant failures (**TABLES 3A, 3B**). Nine patients lost a total of 42 implants in the augmentation group *versus* three patients who lost six zygomatic implants, the difference being borderline statistically significant (difference in proportions = 21.65%; 95% CI: 2.02 to 41.20; P = 0.052).
- Complications (**TABLES 3A, 3B**). Twenty-nine zygomatic patients were affected by 55 complications *versus* 16 augmentation patients (30 complications), the difference being statistically significant (difference in proportions = -30.87 %; 95% CI: -51.88 to -9.86; P = 0.007).
- Quality of life (OHIP-14). The initial OHIP-14 score was 27.58±8.97 in augmentation group patients *versus* 29.29±9.40 in zygomatic implant group patients (**TABLE 4A**). The initial OHIP-14 did not significantly differ between groups (P > 0.05). The OHIP score at 3 years post-loading was 4.11± 7.27 in the augmentation group and 4.51±6.23 in the zygomatic group, with no statistically significant differences between the two (mean difference = 0.40; 95% CI: -2.80 to 3.61; P = 0.624; **TABLE 4B**). Both groups had significantly improved OHIP-14 scores as compared to before rehabilitation (P < 0.01 both for both groups).
- Number of days with totally or partially impaired patient activity. Days of total infirmity were on average 7.42±3.17 for the augmentation group and 7.17±1.96 for the zygomatic group, the difference not being statistically significant (mean difference = -0.25; 95% CI: -1.52 to 1.02; P = 0.692). Days of partial infirmity were on average 14.24±4.64 for the

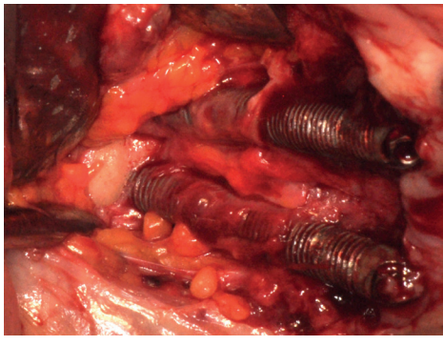

FIG. 4: *Clinical view at implant removal, 3 years after loading, of patient #20 (Dr. Pistilli). The patient suffered of severe peri-implant mucositis that developed into sinusitis at implants on right side. Three cycles of antibiotics and a FESS intervention failed to improve the sinusitis, and both implants had to be removed, despite being stably anchored in the zygomatic bone.*

TABLE 1 MAIN PATIENT AND INTERVENTION CHARACTERISTICS (71 PATIENTS)

	Zygomatic implants (35 patients)	Augmentation + conventional implants (36 patients)
Females (%)	18 (51.4%)	21 (58.3%)
Age (range in years)	58.31 (43–74)	57.58 (36–71)
Non-smoker	22 (62.9%)	23 (63.9%)
Smoking up to 10 cigarettes/day	3 (8.6%)	8 (22.2%)
Smoking more than 10 cigarettes/day	10 (28.6%)	5 (13.9%)
Severely atrophic maxilla (no possibility to place conventional implants)	29 (82.9%)	23 (63.9%)
Atrophic maxilla (possibility to place 2 frontal implants)	6 (17.1%)	13 (36.1%)
General + local anaesthesia	35 (100.0%)	33 (91.7%)
Sedation + local anaesthesia	0 (0.0%)	3 (8.3%)
Both sinus lift and augmentation with blocks/granular bone	NA	19 (52.8%)
Only 1-stage sinus lift	NA	2 (5.5%)
Only 2-stage sinus lift	NA	15 (41.7%)
Total number of implants inserted	141 (37.2%)	238 (62.8%)
Implants inserted with a torque greater than 40 Ncm	136 (96.5%)	158 (66.4%)
Implants inserted with a torque up to 40 Ncm	5 (3.5%)	80 (33.6%)
Zygomatic implants with the neck fully embedded in crestal bone	102 (77.9%)	NA
Zygomatic implants with exposed threads	81 (61.8%)	NA
Zygomatic implants with exposed threads which have been grafted	39 (29.8%)	NA
Number of 8.5-mm long implants	2 (1.4%)	38 (16.0%)
Number of 10-mm long implants	0 (0.0%)	84 (22.2%)
Number of 11.5-mm long implants	4 (2.8%)	42 (17.6%)
Number of 13-mm long implants	4 (2.8%)	46 (19.3%)
Number of 15-mm long implants	0 (0.0%)	28 (11.8%)
Number of 35-mm long implants	7 (5.0%)	NA
Number of 40-mm long implants	25 (17.7%)	NA
Number of 42.5-mm long implants	13 (9.2%)	NA
Number of 45-mm long implants	28 (19.9%)	NA
Number of 47.5-mm long implants	17 (12.1%)	NA
Number of 50-mm long implants	32 (22.7%)	NA
Number of 52.5-mm long implants	9 (6.4%)	NA
Number of 3.4-mm diameter implants	0 (0.0%)	1 (0.4%)
Number of 3.5-mm diameter implants	6 (4.3%)	151 (63.4%)
Number of 3.75-mm diameter implants	2 (1.4%)	0 (0.0%)
Number of 4 mm-diameter implants	131 (92.9%)	NA
Number of 4.3-mm diameter implants	1 (0.7%)	86 (36.1%)
Number of 5-mm diameter implants	1 (0.7%)	0 (0.0%)

NA = not applicable

TABLE 2 OVERALL COMPARISON OF ALL OUTCOME MEASURES AT 3 YEARS POST-LOADING

	Zygomatic group	Augmentation group	Difference	95% CI	P-value
Patients with prosthesis failures	2 out of 33	6 out of 33	18.18%	1.44 to 34.91	0.082
Patients with implant failures	3 out of 32	9 out of 29	21.65%	2.02 to 41.20	0.052
Patients with complications	29 out of 35	16 out of 31	-30.87%	-51.88 to -9.86	0.007*
OHIP-14 scores	N = 35; 4.51±6.23	N = 36; 4.11±7.27	0.40	-2.80 to 3.61	0.624
Days of total infirmity	N = 35; 7.17±1.96	N = 33; 7.42±3.17	-0.25	-1.52 to 1.02	0.692
Days of partial infirmity	N = 35; 12.17±3.82	N = 33; 14.24±4.64	-2.07	-4.12 to -0.02	0.048*
Days to functional loading	N = 35; 1.34±2.27	N = 33; 444.32±207.86	-442.98	-513.10 to -372.86	<0.001*
Number of dental visits	N = 34; 20.05±6.23	N = 28; 23.00±11.80	-2.94	-7.62 to 1.74	0.213

**Statistically significant differences*

TABLE 3A DESCRIPTION OF PROSTHESIS FAILURES, IMPLANT FAILURES AND COMPLICATIONS IN THE ZYGOMATIC GROUP, IN CHRONOLOGICAL ORDER UP TO 3 YEARS AFTER LOADING

PROSTHESIS FAILURES			
Patient/centre	**Timing**	**Description**	**Outcome**
Patient 15/Bologna	3w pl	Lost 3 zygomatic implants out of 4 with the provisional prosthesis	Back to old denture
Patient 20/Bologna	3y pl	Lost 2 zygomatic implants from the right side out of 4 with the prosthesis	Adaptation of the prosthesis
IMPLANT FAILURES			
Patient 15/Bologna	2–5w pip	Day 12 post-loading the posterior left zygomatic implant was mobile (removed) Prosthesis fitted on the 3 remaining implants Week 3 post-loading prosthesis mobile: both anterior zygomatic implants were mobile (removed) Posterior right zygomatic implant had 2 mm anteroposterior mobility (kept in place)	Not replaced
Patient 2/Rome	10m pl	Lost one posterior left zygomatic implant (painful & mobile)	Not replaced
Patient 20/Rome	3y pl	Removed 2 zygomatic implants from the right side out of 4 due to sinusitis (**FIG. 4**)	Not replaced
COMPLICATIONS			
Patient 11/Bologna	Implantation 34m pl	Sinus epithelium perforation on left side Detachment of #21 from the provisional prosthesis	Evolution membrane placed Repaired chairside
Patient 13/Bologna	Implantation	Sinus epithelium perforation on left side	Evolution membrane placed
Patient 2/Rome	Implantation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 3/Rome	Implantation	Sinus epithelium perforation on left side	Evolution membrane placed

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Patient 4/Rome	Pip 19m pl 3y pl	Major swelling also involving the lower lip Peri-implant mucositis at right side implants Abutment screw at right distal implant fractured	Healed spontaneously in 2 weeks Scaling with ultrasound and flushing with chlorhexidine and H_2O_2. Patient recalled every 2 months Replaced
Patient 15/Bologna	2–5w pip	Day 12 post-loading the posterior left zygomatic implant was painful and mobile Week 3 post-loading both anterior zygomatic implants were painful and mobile	3 implants removed + antibiotic therapy
Patient 10/Bologna	3w pip 30m pl	Major swelling under the right eye Peri-implant mucositis at mesial right implant	Amoxicillin + clavulanic acid 875/125 mg every 8 hours for 10 days + pain killers; recurrence after 2 weeks – exploratory surgery revealed necrotic Bichat's fat pad in the sinus; removed + amoxicillin + clavulanic acid 875/125 mg every 8 hours for 10 days + pain killers – resolved Scaling with ultrasound and flushing with chlorhexidine and H_2O_2. Patient recalled every 2 months
Patient 16/Spain	1m pip	Sinusitis	Improved with amoxicillin-clavulanic acid 875/125 mg every 8 hours for 1 month and nasal rinses with isotonic seawater (Rhinomer); persistent cacosmia in right nasal fossa that slowly disappeared on its own
Patient 1/Spain	1m to 4m pip	Zygoma and periorbital infection evolved into chronic fistula	Cutaneous debridement + levofloxacin 500 mg/day for 10 days + implant apex resection – resolved
Patient 20/Spain	1m pip	Headache	Resolved spontaneously
Patient 25/Spain	1m pip 4m pip 4m pip	Right maxillary sinusitis Right maxillary tumefaction Peri-implant mucosa recessions at frontal implants	Amoxicillin-clavulanic acid 875/125 mg every 8 hours for 7 days Amoxicillin-clavulanic acid 875/125 mg every 8 hours for 7 days – resolved Not treated
Patient 3/Spain	2m pip	Right maxillary sinusitis	Amoxicillin-clavulanic acid 875/125 mg every 8 hours for 1 week – resolved
Patient 4/Bologna	3m pip	Peri-implant mucositis + fistula at anterior left zygomatic implant	Prosthesis removal and debridement - healed after 1 week + maintenance every 2 months

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Patient 9/Spain	4m pl	Peri-implantitis at left side implants and abutment screw loosening	1g amoxicillin/clavulanic acid 3x day for 1 month, afterwards asymptomatic. No radiographic signs of sinusitis
	10m pl	Abutment screw loosening and pain in the left maxillary sinus, with no tumefaction	500 mg amoxicillin/clavulanic acid 3x day for 1 month, afterwards asymptomatic. No radiographic signs of sinusitis.
	27m pl	Left maxillary sinusitis and abutment screw loosening	1g amoxicillin/clavulanic acid 3x day for 2 weeks.
	30m pl	Left maxillary sinusitis and abutment screw loosening	500 mg amoxicillin/clavulanic acid + 500 mg metronidazole 3x day for 2 weeks
	32m pl	Bilateral sinusitis and abutment screw loosening	500 mg amoxicillin/clavulanic acid + 500 mg metronidazole 3x day for 2 weeks and 42m pl functional endoscopic sinus surgery (FESS)
Patient 4/Spain	5m to 3y pl	Right maxillary sinusitis with fistula next to implant 13	Right FESS and endoscopic septoplasty 8 months after implant placement. Good evolution until 6 months later, when symptoms reappeared New FESS 31 months after implant placement. 2 weeks after right nasal fossa epistaxis that required surgical endoscopic cauterization. 3 months later right maxillary sinusitis reappeared
Patient 20/Spain	9m pl	Vestibular exposure of implant threads in 23, with pus and headache	Implant threads removal + connective tissue graft from palate – resolved
Patient 2/Rome	10m pl	Posterior left zygomatic implant painful and mobile	Removed
Patient 5/Bologna	11m pl	Fracture of the resin prosthesis lining	Repaired chairside
	2y pp	Peri-implant mucositis at mesial right implant	Scaling with ultrasound and flushing with chlorhexidine and H_2O_2. Patient recalled every 2 months
Patient 3/Bologna	12m pl	Fracture of the MUA abutment screw of the left anterior standard implant	Removed, also using ultrasound, and replaced
Patient 17/Spain	12m pl	Discomfort in the anterior wall of the maxilla, swelling and fistula at implant 16. Pain at #26 upon pressure with finger	Amoxicillin-clavulanic 875/125 mg every 8 hours for 1 week + chlorhexidine gel – resolved
Patient 1/Rome		Peri-implant mucositis at distal left implant	Scaling with ultrasound and flushing with chlorhexidine and H_2O_2. Patient recalled every 2 months
Patient 20/Bologna	31m pl	Severe peri-implant mucositis developing into sinusitis at right side implants	3 cycles with of amoxicillin+ clavulanic acid 1 g 3x7 + metronidazole 250 mg 3x7 + inhalation 2x7 of 2 cc saline + 1 fl betamethasone + 1/2 fl lincomycin 600 mg + 4 drops of Argotone). FESS and, after 3 months, removal of implants (**FIG. 4**)

w = weeks; m = months; y = years; pl = post-loading; pip = post-implant placement. All patients treated at the Italian centres (21 patients), experienced transient (from 1 week to 3 months) paraesthesia of the infraorbital nerves

TABLE 3B DESCRIPTION OF PROSTHESIS FAILURES, IMPLANT FAILURES AND COMPLICATIONS IN THE AUGMENTATION GROUP, IN CHRONOLOGICAL ORDER UP TO 3 YEARS AFTER LOADING

PROSTHESIS FAILURES			
Patient/centre	**Timing**	**Description**	**Outcome**
Patient 19/Spain	2 to 34m pip 15m pl	3 out of 8 implants lost #11 migrated to nasal space 2 months after placement #22 mobile 30 months after placement #24 mobile 34 months after placement #17 lost due to peri-implantitis 13 months after loading #15, 27 and 26 mobile 15 months after loading	Delayed prosthesis placement Back to denture
Patient 1/Bologna	ab	6 out of 6 implants mobile at abutment connection	Back to old denture
Patient 7/Bologna	ab	7 out of 8 implants mobile at abutment connection	Back to old denture
Patient 18/Spain	ab	3 out of 8 implants mobile at abutment connection 3 implants replaced after 6 months	Delayed prosthesis placement
Patient 7/Spain	13m pip	6 out of 8 implants lost due to infection	Placement of 4 zygomatic implants, successfully loaded
Patient 11/Spain	14 to 45m pip	6 out of 8 implants removed	Placement of 4 zygomatic implants, successfully loaded
IMPLANT FAILURES			
Patient 19/Spain	2 to 34m pip 15m pl	3 out of 8 implants lost #11 migrated to nasal space 2 months after placement #22 mobile 30 months after placement #24 mobile 34 months after placement #17 and 23 (new implant) lost due to peri-implantitis 13 months after loading #15, 27 and 26 mobile 15 months after loading	 Spontaneously expelled via the nose New left nasal floor lift + implant 23 placement 35 months after first implant placement Back to denture
Patient 1/Bologna	ab	6 out of 6 implants mobile at abutment connection Patient wore denture from day 20 post-implantation	Back to old denture
Patient 7/Bologna	ab	7 out of 8 implants mobile at abutment connection Patient wore denture from week 2 post-implantation Last implant removed 2 years after placement	Back to old denture Placement of 4 zygomatic implants, successfully loaded
Patient 18/Spain	ab	3 out of 8 implants mobile at abutment connection 1 replaced implant mobile at new abutment connection	3 implants replaced after 6 months
Patient 5/Spain	ab	3 out of 8 implants mobile: #23 mobile at abutment connection #11 mobile 3 months after abutment connection #16 mobile 4 months after abutment connection	All 3 implants replaced 16 months after placement of first implants
Patient 6/Spain	7m pip	Lost implant 16 out of 8 implants	None
Patient 7/Spain	13m pip	6 out of 8 implants lost due to infection	Surgical removal of the infected graft and placement of 4 zygomatic implants
Patient 11/Spain	14m pip	6 out of 8 implants removed #11, 23, 24 and 25 lost 14 months after placement #14 lost 39 months after implant placement #13 removed 45 months after implant placement	 #11 and 26 replaced 22 months after initial placement Placed 2 zygomatic implants in positions 22 and 25, 38 months after first implant placement Replaced by 2 zygomatic implants in positions 12 and 15, 45 months after loading
Patient 24/Spain	16m pl	Implant 16 and 27 explanted due to peri-implantitis	Prosthesis adapted

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COMPLICATIONS			
Patient 5/Spain	Augmentation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 8/Spain	Augmentation 9m pip	Sinus epithelium perforation on right side Exposed vestibular surface of implant 23 at second phase of surgery	Evolution membranes placed Connective tissue graft
Patient 11/Spain	Augmentation	Bilateral sinus epithelium perforation	Evolution membranes placed
Patient 12/Spain	Augmentation	Bilateral sinus epithelium perforation	Evolution membranes placed
Patient 15/Spain	Augmentation	Bilateral sinus epithelium perforation	Evolution membranes placed
Patient 18/Spain	Augmentation 25m pl 32m pl 49m pl	Sinus epithelium perforation on left side Chipping of the prosthesis lining Chipping of the prosthesis lining Chipping of the prosthesis lining	Evolution membrane placed Repaired at dental lab Repaired at dental lab Repaired at dental lab
Patient 22/Spain	Augmentation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 24/Spain	Augmentation 32m pip 3 to 16 m pl	Sinus epithelium perforation on right side Peri-implant bone loss at #15 and 27 at abutment connection Peri-implantitis at implants 16 and 27 and then also at #23 and 26	Placed Evolution membrane placed Curettage and chlorhexidine Curettage, but #16 and 27 had to be explanted
Patient 26/Spain	Augmentation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 6/Bologna	Augmentation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 9/Rome	Augmentation	Sinus epithelium perforation on right side	Evolution membrane placed
Patient 18/Rome	Augmentation	Sinus epithelium perforation on left side	Evolution membrane placed
Patient 7/Spain	Implantation – 13m pip	Onlay block fragmentation when placing implant 24 Left maxilla infected; The infection progressed to the right side until patient lost 6 implants 13 months after their placement	Amoxicillin-clavulanic acid 875/125 bilateral bone graft removal and right maxillary sinus curettage + placement of 4 zygomatic implants
Patient 19/Spain	2m pip 11m pl	Implant 11 migrated into the nasal space Since the patient lost another 2 implants a new nasal floor lift was performed, but the nasal mucosa was perforated on the right side Peri-implantitis at right maxillary implants Peri-implantitis at #17	Spontaneously expelled through nose Right implants could not be placed Improved after curettage and better hygiene Implant removed
Patient 22/Bologna	22 m pl	Chipping of the prosthesis lining	Repaired chairside
Patient 21/Bologna	28 m pl	Chipping of the prosthesis lining	Repaired chairside

w = weeks; m = months; y = years; pl = post-loading; pip = post-implant placement; ab = abutment connection

TABLE 4A OHIP-14 SCORES AT BASELINE, BEFORE COMMENCING WITH THE IMPLANT-SUPPORTED PROSTHESIS REHABILITATION

How often in the last year have you had problems with your upper prosthesis?		
Question	**Zygomatic group (n = 35)**	**Augmentation group (n = 36)**
OH1: Have you had trouble pronouncing any words?	2.26±1.48	2.67±1.10
OH2: Have you felt that your sense of taste has worsened?	2.20±1.18	2.53±1.11
OH3: Have you had painful aching in your mouth?	2.06±1.03	1.64±1.02
OH4: Have you found it uncomfortable to eat any foods?	3.37±1.06	3.17±1.06
OH5: Have you felt self-conscious?	2.80±1.08	2.50±1.11
OH6: Have you felt tense?	2.14±1.00	2.00±1.04
OH7: Has your diet been unsatisfactory?	2.46±1.15	2.69±1.24
OH8: Have you had to interrupt meals?	2.23±1.06	2.17±0.97
OH9: Have you found it difficult to relax?	2.06±1.24	1.64±1.10
OH10: Have you been a bit embarrassed?	2.26±1.20	2.28±1.19
OH11: Have you been a bit irritable with other people?	0.94±0.97	0.83±0.74
OH12: Have you had difficulty doing your usual jobs?	1.57±1.36	1.06±1.17
OH13: Have you felt that life in general was less satisfying?	2.06±1.11	1.61±1.15
OH14: Have you been totally unable to function?	0.89±0.76	0.81±0.75
Total score	29.29±9.40	27.58±8.97

Data are presented as mean±standard deviation. Possible answers: 0 (never), 1 (hardly ever), 2 (occasionally), 3 (very often) to 4 (fairly often)

TABLE 4B OHIP-14 SCORES ASSESSED AT 3-YEAR AFTER INITIAL LOADING

How often in the last year have you had problems with your upper prosthesis?			
Question	**Zygomatic implants (n = 35)**	**Augmention group (n = 36)**	**P-value**
OH1: Have you had trouble pronouncing any words?	0.59±0.83	0.61±0.63	0.577
OH2: Have you felt that your sense of taste has worsened?	0.25±0.67	0.19± 0.56	0.676
OH3: Have you had painful aching in your mouth?	0.59±1.07	0.30±0.67	0.358
OH4: Have you found it uncomfortable to eat any foods?	0.78±0.90	0.57±0.80	0.331
OH5: Have you felt self-conscious?	0.56±0.84	0.65±1.12	0.934
OH6: Have you felt tense?	0.53±0.71	0.80±0.89	0.240
OH7: Has your diet been unsatisfactory?	0.34±1.01	0.30±0.67	0.730
OH8: Have you had to interrupt meals?	0.50±0.71	0.53±0.70	0.773
OH9: Have you found it difficult to relax?	0.31±0.53	0.53±0.70	0.209
OH10: Have you been a bit embarrassed?	0.25±0.56	0.34±0.84	0.905
OH11: Have you been a bit irritable with other people?	0.06±0.24	0.26±0.66	0.225
OH12: Have you had difficulty doing your usual jobs?	0.00±0.00	0.07±0.27	0.113
OH13: Have you felt that life in general was less satisfying?	0.03±0.17	0.30±0.78	0.091
OH14: Have you been totally unable to function?	0.12±0.42	0.15±0.46	0.789
Total score	4.51±6.23	4.11±7.27	0.624

Data are presented as mean±standard deviation. Possible answers: 0 (never), 1 (hardly ever), 2 (occasionally), 3 (very often) to 4 (fairly often)
**All changes from baseline statistically significantly different in both groups (P < 0.01)*

augmentation group and 12.17±3.82 for the zygomatic group, the difference being statistically significant (mean difference = -2.07; 95% CI: -4.12 to -0.02; P = 0.048).

- Time to function. The mean number of days to receive a functional prosthesis were 444.32±207.86 for augmentation patients and 1.34±2.27 for zygomatic patients, the difference being statistically significant (mean difference = -442.98; 95% CI: -513.10 to -372.86; P < 0.001).
- Number of sessions. The average number of dental appointments was 23.00±11.80 for augmentation patients and 20.05±6.23 for zygomatic patients, the difference not being statistically significant (mean difference = -2.94; 95% CI: -7.62 to 1.74; P = 0.213).

A comparison of the clinical outcomes among the three treating surgeons is presented in **TABLE 5**. There were differences among surgeons for days with total impaired activity (P = 0.010; with significantly more days of impaired activity in the Spanish group than the Rome group) and number of dental visits (P = 0.009; with a higher number of visits in the Spanish group than in both Italian groups).

DISCUSSION

This trial was designed to elucidate whether it would be preferable to rehabilitate edentulous patients with atrophic maxillae by either performing bone augmentation procedures with bone substitutes and delayed placement of conventionally loaded standard dental implants or using immediately loaded zygomatic implants. Despite revealing more complications at zygomatic implants, interpretation of the overall data suggests a more favourable outcome for zygomatic implants, since fewer implant and prosthesis failures occurred, and patients could be rehabilitated within a couple of days when using zygomatic implants *versus* an average of 15 months when augmented. Even though the difference in implant failures had just borderline significance, it should be considered that it was calculated at the patient level. At implant level, the number of conventional implants lost was far higher (42 conventional implants lost *versus* only 6 zygomatic implants), which implies considerable clinical significance.

TABLE 5 COMPARISON OF THE CLINICAL OUTCOMES AMONG THE THREE TREATING SURGEONS AT 3 YEARS POST-LOADING

	Spain	Dr. Felice (Bologna)	Dr. Pistilli (Rome)	P-value
Number of treated patients	27	24	20	NA
Drop-out	2	6	2	0.138
Patients with failed prostheses	5	5	0	0.084
Patients with failed implants	7 (28 implants)	4 (19 implants)	1 (1 implant)	0.225
Patients with failed augmentation procedures	0 out of 13	1 out of 14	0 out of 10	0.653
Patients with complications	19 (43 complications)	13 (25 complications)	13 (20 complications)	0.506
Mean OHIP 14 score	6.66±8.93	3.04±5.78	2.65±2.13	0.560
Mean total infirmity days	8.44±3.18	7.04±2.27	6.16±1.42	0.010*
Mean partial infirmity days	14.32±5.40	12.61±4.34	12.40±2.21	0.252
Mean days to functional loading	270.09±375.90	157.14±166.76	162.30±165.56	0.281
Average number of appointments	26.04±13.45	19.45±4.80	18.2±3.10	0.009*§

*Data are presented as mean±standard deviation. NA: not applicable. Significant comparisons: *Spain vs Dr. Pistilli; §Spain vs Dr. Felice*

Obviously, these results apply only up to the third year after loading, and it would be sensible to wait for longer follow-ups (up to 10 years) before drawing definitive conclusions; indeed, there was an appreciable increase in the number of sinusitis over time in the zygomatic implant group. This phenomenon might be associated with the presence of threads and the rough surface of the coronal portion of the zygomatic implants, which may favour plaque accumulation and retention, thereby facilitating the onset of peri-implant mucositis; this could gradually transform into peri-implantitis, and ultimately evolve into sinusitis once the infection reaches the sinuses. The cases we encountered were recurrent and very difficult to be treat.

Another source of the significantly more complications reported for zygomatic implants was linked to the presence of post-operative paraesthesia at both infraorbital nerves, which affected all patients treated at both Italian centres but none at the Spanish centre. A plausible explanation for this difference is potential differences in surgical technique, with the Italian surgeons opening wider flaps to better expose the zygomatic bone. Plus, the Italian centres were less experienced with zygomatic implants than the Spanish centre. All cases of paraesthesia were transient, ranging from 1 week to 3 months, and resolved spontaneously.

Patient quality of life, measured via the OHIP-14 score, significantly improved with both rehabilitation procedures, and there were no major difference between the two alternatives in this regard.

Days with total infirmity were similar in both groups, most likely depending on the major surgical interventions performed under general anaesthesia, whereas an average of two days less of partial infirmity was reported by patients rehabilitated with zygomatic implants, the difference being statistically significant. On average, patients rehabilitated with zygomatic implants required three fewer appointments than augmentation group patients (20 *versus*, 23 visits), but the difference was not statistically significant.

Unfortunately, at the 4-month post-loading follow-up, 35 patients from the Italian centres were not rehabilitated with a definitive prosthesis as planned at the protocol stage. This was due to a misunderstanding between the Italian centres and Nobel Biocare. Specifically, the Italian centres did not ask for the definitive abutments and definitive titanium Procera frameworks as agreed in the protocol stage, thinking that patients had to pay for their definitive prostheses entirely by themselves. As a consequence, 35 patients were not able or willing to pay for the definitive prosthesis. As soon as the misunderstanding emerged, patients were called back and offered the definitive prostheses, and were only charged the dental technician's costs for lining the titanium frameworks with composite-resin or ceramic.

Despite the good overall clinical performance of zygomatic implants, some unpleasant complications did arise, especially sinusitis, that could not be successfully treated, suggesting that their use should be limited to patients with severely atrophic maxillae. It is not possible to compare these results with those of similar RCTs, as none are yet available. The only other RCT on zygomatic implants published to date compared the use of rotational drills *versus* piezo-surgery using specifically designed inserts to prepare the sites for zygomatic oncology implants in a split-mouth trial[9,14].

The main limitations of the present investigation were the small number of patients included, albeit sufficient to provide some useful indications and generate hypotheses for future investigations, and the poor adherence to the research protocol regarding periapical radiographs for assessing peri-implant marginal bone level changes. That being said, both procedures were tested under real clinical conditions, and patient inclusion criteria were broad, and the results of the present trial can therefore be generalised to larger populations with similar characteristics. Nonetheless, it is important to bear in mind that placement of zygomatic

implants is a complex procedure requiring skilled and experienced operators, since potentially severe complications may occur.

CONCLUSIONS

On the one hand, three-year post-loading data suggest that immediately loaded zygomatic implants are associated with fewer prosthesis failures (two *versus* eight patients), implant failures (three patients lost 6 zygomatic implants *versus* nine augmentation patients who lost 42 implants) and time needed for functional loading (1.3 days *versus* 444.3 days) as compared to augmentation procedures and conventionally loaded dental implants. On the other hand, significantly more complications were reported at zygomatic implants, and there was an apparent increase in severe sinusitis at zygomatic implants over time. Hence, long-term data are required, but in the short-term, zygomatic implants proved to be a better means of rehabilitating severely atrophic maxillae.

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