Official Title:
A resorbable versus a non-resorbable bone substitute at immediate post-extractive single implants immediately loaded: a multicentre randomised controlled trial

Brief Title:
Resorbable vs non-resorbable bone substitute at immediate post-extractive single implants

NCT Number:

NCT07047131

Unique Protocol ID:

2301201902319

Date of the Document:

December 18, 2018

A resorbable versus a non-resorbable bone substitute at immediate post-extractive single implants immediately loaded: a multicentre randomised controlled trial

Introduction

A systematic review did not show statistically significant differences between immediate, immediate-delayed and delayed implant placement protocols in terms of performance due to the poor quality of the available clinical data and underpowered study designs(1). The use of bone substitute can improve aesthetics at post-extractive implants(2). Bone substitutes can be poorly resorbable (semi-degradable), meaning the they simply preserve bone volume being integrated into newly-formed bone or can be rapidly resorbed (fully degradable) and replaced by new autogenous bone. It is currently unknown if one of the two mechanisms is preferable at immediate post-extractive implants.

Aims

To compare the effectiveness of a partly versus a fully resorbable bone substitute at immediate post-extractive single implants.

Study Design

Multicentre, single blind, randomised controlled trial of parallel group design where a partly resorbable bone substitute (Apatos) will be compared to a fully resorbable bone substitute (GTO) to fill bone-to implant gaps at immediate post-extractive implants.
Each patient will provide only one implant site. For patients with multiple teeth to be extracted, the operator will be free, at the screening visit, to select one future implant site to be included in the trial. The trial will have a duration of 5-year post-loading.

- Randomisation: using computer generated random numbers, centralized with sequentially sealed opaque envelopes provided by the study adviser (Marco Esposito).
- Allocation concealment: the operator will know about the type of graft to place at the implant to bone gap by opening a sealed envelope after the immediate implant has been placed and definitively included in the study.
- Blinding: independent and blind assessors will assess implant stability. Bone level changes, volumetric change and aesthetic evaluation will be done by a single blinded and independent assessor.

The principles outlined in the Declaration of Helsinki on clinical research involving human subjects will be adhered to. A written informed consent will be obtained for each patient. The study got the approval of the ethical committee King Juan Carlos University, Madrid, Spain

The trial will be reported according to the CONSORT statement for improving the quality of reports of parallel-group randomized trials (http://www.consort-statement.org/).

Inclusion criteria at screening

- Any patient requiring at least one single immediate post-extractive implant.
- At least 18 year old, able to understand and to sign an informed consent

- There must be sufficient bone to allow the placement of at least a 3.5 mm diameter and 8.5 mm long implant.
- After tooth extraction there must be a potential gap of at least 2 mm from the buccal inner bone plate and the implant surface.

Exclusion criteria at screening
- General contraindications to implant surgery.
- Immunosuppressed or immunocompromised patients.
- Patients irradiated in the head and/or neck.
- Uncontrolled diabetes.
- Pregnancy or lactation.
- Active periodontal disease
- Poor oral hygiene and motivation.
- Addiction to alcohol or drugs.
- Psychiatric problems and/or unrealistic expectations
- Patients with an acute infection (abscess) in the site intended for implant placement.
- Patients unable to commit to a 5-year follow-up.
- Patients treated or under treatment with intravenous amino-bisphosphonates.
- patients referred only for implant placement if follow-ups cannot be done at treatment centre.
- Patients participating in other studies, if the present protocol could not be fully adhered to. In case of doubts please contact Marco Esposito (espositomarco@hotmail.com).

Exclusion criteria after tooth extraction
- More than 4 mm in height of missing buccal wall, assessed using the highest peak of palatal wall as reference point.
- Less than 2 mm of space between the inner plate of the buccal bone and the implant surface.

Centre and main operator

King Juan Carlos University, Madrid, Spain
Treating surgeon: Dr David Madruga Gonzales (dr.davidmadruga@gmail.com)
Masked local outcome assessor: Dr Angel Lopez Carpintero

Study population and number of patients to be included
Prior to enrolment, all patients will be asked to sign an informed consent form to document that they understood the scope of the study (including procedures, follow-up evaluations, and any potential risks involved), were allowed an opportunity to ask questions pertaining to this study and were apprised of treatment alternatives. The study is open to qualifying patients without regard to sex or race.

Sample size
In this study, the primary comparison is the effectiveness of different bone substitutes in maintaining bone volumes, therefore, the sample size calculation will be based on bone volumes.
To detect a difference of 5 mm^3 in bone volume changes between the two bone substitutes (standard deviation of 6.96 mm^3(3)) with a two-side 5% significance level and a power of 80%, a total sample size of 80 patients will be necessary, given an anticipated dropout rate of 20%.
We can contribute with 50 patients (25 per group).

Outcome measures

Primary outcome variable

Volume changes of the volume changes of the peri-implant tissues will be evaluated by taking a limited view cone-beam computed tomography (CBTC) of the area of interest at implant placement, 1 and 5 years after loading.

Secondary outcome variables

Crown/implant failure: whether it will not be possible to place the crown because of implant failure or secondary to implant failure, and replacement of the crown for any reason. Implant failure is defined as implant mobility and/or any infection dictating implant removal and any mechanical complications rendering the implant unusable (e.g. implant fracture). The stability of each individual implant will be measured by the blinded outcome assessor manually by assessing the stability of the crown using the handles of two metallic instruments at 1 and 5 years after loading.

Biological and biomechanical complications: will be recorded and reported by study group. Examples of biological complications are: fistula, peri-implantitis. Examples of biomechanical complications are fracture of the metal screws, loosening of the crown, fracture of the ceramic lining.

Peri-implant marginal bone level changes: periapical digital radiographs will be made with the paralleling technique at implant placement, at 1 and 5 years of loading. In case of an unreadable radiograph, the radiograph must be made again. Peri-implant marginal bone levels will be measured using the Image J (National Institutes of Health, Bethesda, Maryland, USA) software. The software will be calibrated for every single image using the known implant length or, if the full implants is not visible on the radiograph, the implant diameter. Measurements of the mesial and distal bone crest level adjacent to each implant will be made to the nearest 0.01 mm. Reference points for the linear measurements will be: the coronal margin of the implant collar and the most coronal point of bone-to-implant contact. Bone levels will be measured at both mesial and distal sides and averaged. Bone level at single implants will be averaged at group level.

Aesthetic evaluation of the clinical pictures taken at delivery of the final crown (baseline), at 1- and 5-year follow-ups, on a computer screen by an independent blinded dentist. The pictures of the vestibular and occlusal aspects must include the two adjacent teeth. The aesthetic evaluation will be done following the pink aesthetic score (4).

Materials

Bone substitutes: the non-resorbable bone substitute is composed by porcine bone granules of cortical bone (Apatos Cortical®, OsteoBiol®, Tecnoss®, Giaveno, Italy) that will be stabilized by a thermogelling synthetic copolymer with type I and III collagen gel (TSV Gel®, OsteoBiol®, Tecnoss®). The resorbable bone substitute is composed by collagenated heterologous cortico-

cancellous porcine bone mix + TSV Gel (GTO®, OsteoBiol®, Tecnoss®). No other grafting material can be used.

- Implant types:
CM Alvim (Neodent, Straumann, Basel, Switzerland) tapered cylindrical threaded bone level implants with cone-morse connection. The implant is made of titanium grade 4 cold-worked and its surface was roughened using sandblasting and acid etching (NeoPoros surface). The operator will be free to choose implant lengths (8.0, 10.0, 11.5 and 13 mm long) and diameters (3.5 and 4.3 mm) according to clinical indications and his preferences.

- Definitive crowns: Screw-retained metal-ceramic crowns.

Clinical procedures
Screening visit (APPENDIX 1)
Potentially eligible patients are screened to establish their eligibility for the study. Please complete APPENDIX 1 (Patient eligibility CRF) and record the number and reason of non-included patients. Patients must be informed on the nature of the study and must sign an informed consent in their own language. Preoperative radiographs must be obtained for every included patient. Investigators are free to choose the most appropriate radiographic examination according to the clinical case (periapical, panoramic, CBCT scans, etc.).
After determining that the patient is qualified for the study, and informed consent has been given, a thorough oral examination will be performed to assess health status, identify oral pathologies that require treatment prior to implant therapy, and analyse available bone over vital structures and adjacent to remaining natural teeth. To record a visual baseline, preoperative intraoral facial and occlusal digital photographs will be made of each patient to document the condition of the dental anatomy and state of soft tissue health.

Patients will be categorised into: 1) non-smokers; 2) moderate smokers (up to 10 cigarettes/day); 3) heavy smokers (more than 10 cigarettes/day), according to what they declare.

OPERATIVE PROCEDURES
Please complete APPENDIX 2 (Surgical and prosthetic CRF)
Prophylactic therapy: Scaling 2-3 days before surgery.
Amoxicillin 2 g one hour prior to tooth extraction and implant placement. Patients allergic to penicillin will be prescribed clindamycin 600 mg 1 hour prior to the interventions. Patients will rinse with chlorhexidine mouthwash 0.2% for 1 minute prior to the intervention.

Local anaesthesia: Articain with adrenaline 1:100.000.

Tooth extraction: Tooth extractions should be performed as atraumatically as possible attempting to preserve the buccal alveolar bone. Extraction sockets must be carefully cleaned from any remains of granulation tissue.

Immediate post-extractive implant installation technique: Drills with increasing diameters will be used to prepare the implant site as suggested by the manufacturers.
Implant sites will be underprepared of at least 1 twist drill size and implants will be inserted with the motor set at a 35 Ncm torque, to ensure adequate implant primary stability.

The choice of the implant diameter and length will be recorded. Implants will be placed slightly subcrestally, about 2 mm below the most apical bone peak, and slightly palatally. Cover screws will be placed. If there is sufficient buccal wall (no more than 4 mm of bone loss and the gap between the buccal wall and the implant is of at least 2 mm, the patient will be finally included in the study.

Disclosure of the randomised allocation

Once the implant has been placed and whether there is sufficient buccal bone (no more than 4 mm of buccal bone loss using the highest peak of palatal wall as reference point) and in the presence of an implant to buccal bone gap of at least 2 mm, the operator will know whether the bone to implant gap will be filled with a semi- or a fully-degradable bone substitute by opening the corresponding sealed envelope. It is absolutely forbidden to open the envelope containing the random code before. The surgeon will write on the Surgical and prosthetic CRF (APPENDIX 2) the patient sequential number contained in the envelope and to which of the two groups the patient is allocated.

Any residual gap between the implant surface and the socket walls will be filled with the bone substitute type as decided by the random allocation procedure. No other type of bone grafting material is allowed. Baseline periapical and limited view CBCT radiographs must be taken. If peri-implant marginal bone levels are difficult to be assessed, a second periapical radiograph will be taken. Implants achieving a torque of at least 35 Ncm will be loaded immediately while those implants placed with less than 35 Ncm will be covered with a standard (0.5 mm thick) collagen membrane of equine pericardium origin (Evolution®, OsteoBiol®, Tecnoss®) and submerged unloaded for 4 months. After 4 months they will be rehabilitated following the same procedures as all other study implants.

Post-surgical instructions and follow-ups

- Postoperative antibiotics will be prescribed: Amoxicillin 1 g 3 times a day for 6 days. Patients allergic to penicillin will be prescribed clindamycin 300 mg thrice a day for 6 days.
- Ibuprofen 400 mg will be prescribed to be taken 2 to 4 times per day, but patients will be instructed not to take it in absence of pain.
- Chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks.

Prosthetic procedures

An impression with the pick-up impression copings will be made with a polyether material.
Within 2 weeks, a definitive metal-ceramic screw-retained crown will be delivered on definitive titanium abutments.
- Periapical radiographs must be made. If the peri-implant marginal bone levels are not readable a second radiograph must be taken.
- Buccal and occlusal pictures of the implant including one adjacent tooth per side must be made.

1 year after loading (APPENDIX 2):

- Crowns will be manually tested for stability.
- Periapical radiographs must be made. If the peri-implant marginal bone levels are not readable a second radiograph must be taken.
- Buccal and occlusal pictures of the implant including one adjacent tooth per side must be made.
- A limited view CBCT of the study implant must be taken.

5 years after loading (APPENDIX 2):
- Crowns will be manually tested for stability.
- Periapical radiographs must be made. If the peri-implant marginal bone levels are not readable a second radiograph must be taken.
- Buccal and occlusal pictures of the implant including 1 adjacent tooth per side must be made.
- A limited view CBCT of the study implant must be taken.

All patients will be recalled every 6 months for professional maintenance. If necessary, the number of maintenance visits can be increased.

In case of suspected implant loss, peri-implantitis, fistula, etc., observed during any of the scheduled visit or during an emergency visit, intraoral radiographs and clinical pictures must be taken and the "Complications, protocol deviation and drop-out CRF" (APPENDIX 3) should be filled in.

Time	
Day 1	photos/extraction/implant placement/patient inclusion/photos/group allocation/augmentation/impression/rx/CBCT
Within week 2	definitive crown delivery/photos
1 year after loading	implant stability/impressions/rx/CBCT/photos/maintenance
5 years after loading	implant stability/impressions/rx/CBCT/photos/maintenance

Drop-outs

All drop-outs should be reported and the reason for dropping out should be investigated and reported per study group. No included patient can be excluded for any reasons by the clinical investigators.

Statistical analysis

All data analysis will be carried out according to a pre-established analysis plan by a dentist with expertise in statistics blinded to group allocation. Descriptive statistics will be performed using mean and standard deviation for quantitative data and frequency and percentage for qualitative data. All-important harms or unintended effects in each group will be reported. The statistical unit of the analysis will be the patient. The primary outcome variable will be volume changes between baseline and 1- and 5-year after augmentation.

For volumetric analysis, an intra-rater agreement study will be performed on the operator to test his reliability. A set of 20 volumetric changes will be evaluated twice with a two-week interval between the measurements. The operator will be considered reliable if the intraclass coefficient of correlation is greater than 0.75.

A comparison of the baseline characteristics between groups will be presented. Differences in the proportion of dichotomous outcomes (e.g. prosthesis and implant failures, complications) will be compared between the groups using a chi-square test. Mean differences between groups for continuous outcomes (e.g. peri-implant marginal bone level changes, PES scores and volumetric analysis) will be compared using an independent sample t-test for pairwise comparisons. Comparisons between each time points and the baseline measurements will be made by paired t-tests, to detect any changes in marginal peri-implant bone levels for each study group.

All statistical comparisons will be conducted at the 0.05 level of significance and estimate, standard error, 95% confidence intervals and P-value will be reported for each term of the models.

In the case of early implant failure or complication the volumetric change will be measured anyway.
The statistical analysis will be intention-to-treat and deviation from the protocol will be considered according to the randomization scheme: all participants will be included in the analysis regardless of adherence to the protocol. In any case, if large deviations from the protocol are generated, a sensitivity per-protocol analysis will be performed.

Administrative procedures and data management
The centre is required to keep complete clinical records and study forms for all patients included in the study. Case report forms (CRFs) should be filled in at the time of data collection. Complete CRFs, and disks containing the digitized clinical pictures and radiographs should be attached to the study folder of each patient.
All data requested for this study will be collected using paper CRFs. The CRFs will be stored in a secure locked place to which only the principal investigator and the responsible for data collection will have access to. Data will also be accessible to Dr Marco Esposito and Tecnoss for monitoring purpose at their discretion. After completion of the various follow-up points (delivery of the final crowns, 1 and 5 years after loading) copies of all the CRFs will be sent to Dr Marco Esposito who will check the data and store them in a computer secured with a password known to him only. Data will be processed by a dentist with expertise in statistics (to be decided) under supervision of Dr Marco Esposito. Patient identity will be protected and known only to the study participants listed in the present protocol.

Protocol amendments and violations
Amendments to this protocol may be necessary and violations to the protocol are likely to occur. Any violation of the protocol should be reported in the "Complications, protocol deviation and drop-out CRF" (APPENDIX 3). In case of problems please contact the study coordinator without delay.

Case report forms (CRFs)
- Patient informed consent form
- Patient eligibility CRF (APPENDIX 1)
- Surgical, prosthetic and follow-up CRF (APPENDIX 2)
- Complications, protocol deviation and drop-out CRF (APPENDIX 3)

REFERENCES
1. Esposito M, Grusovin MG, Polyzos IP, Felice P, Worthington HV. Interventions for replacing missing teeth: dental implants in fresh extraction sockets (immediate, immediate-delayed and delayed implants). Cochrane Database of Systematic Reviews 2010: Chichester, UK: John Wiley & Sons, Ltd.
2. De Angelis N, Felice P, Pellegrino G, Camurati A, Gambino P, Esposito M. Guided bone regeneration with and without a bone substitute at single post-extractive implants: 1-year post-loading results from a pragmatic multicentre randomised controlled trial. European Journal of Oral Implantology 2011;4:313-325.
3. Thalmair T, Fickl S, Schneider D, Hinze M, Wachtel H. Dimensional alterations of extraction sites after different alveolar ridge preservation techniques - a volumetric study. Journal of Clinical Periodontology 2013;40:721-727.
4. Fürhauser R, Florescu D, Benesch T, Haas R, Mailath G, Watzek G. Evaluation of soft tissue around single-tooth implant crowns: the pink esthetic score. Clinical Oral Implants Research 2005;16:639-644.