Official Title:
7 mm versus 5 mm diameter immediate post-extractive implants in the molar region: a multicentre randomised controlled trial

Brief Title:
Comparing 7 mm and 5 mm Implants Placed Immediately After Molar Extraction

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Aims

To compare the effectiveness of 7.0 mm-wide diameter implants with 5.0 mm-conventional diameter implants placed immediately after tooth extraction in the molar region.

Test hypothesis: there is no difference in clinical outcomes between the two procedures, against the alternative hypothesis of a difference.

Study Design

Multicenter randomized controlled trial (RCT) of parallel group design. Each patient will provide only one implant-supported crown. For patients with multiple teeth to be extracted, the operator will be free, at the screening visit, to select the tooth to be included in the trial. The trial will have a duration of 5 years post-loading.

- Randomisation: using computer generated random numbers, centralized with sequentially sealed opaque envelopes provided by the study adviser.
- Allocation concealment: operators will know about the intervention to be delivered by opening a sealed envelope after the tooth has been extracted.
- Blinding: independent and blind assessors at each centre will assess implant stability. Bone level changes and aesthetic evaluation will be done by a single blinded and independent assessor who will evaluate the outcomes of all centers.

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 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

Any patient requiring at least one single immediate post-extractive implant in the posterior jaw (molar areas only), being at least 18 year old and able to sign an informed consent. There must be sufficient bone to allow the placement of an implant at least a 7 mm-wide and 7 mm-long.

Preoperative radiographs have to be taken. Investigators are free to choose the most appropriate examination according to the clinical case (intra-oral, panoramic, CT scans, etc.).

Patients will be grouped 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.

Exclusion criteria

- 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.
- Patients with an acute infection (abscess) in the site intended for implant placement.
- Necessity to lift the maxillary sinus.
- Patients unable to commit to a 5-year follow-up.
- Patients treated or under treatment with intravenous amino-bisphosphonates.
- Lack of bony walls surrounding the future implant.
- Patients participating in other studies, if the present protocol could not be fully adhered to. In case of doubts please contact the study coordinator.

Study population and number of patients to be included

Prior to enrollment, all patients will be asked to read and if they understood it, to sign an informed consent form to document that they understand the scope of the study (including procedures, follow-up evaluations, and any potential risks involved), were allowed 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. Seventy patients will be included, 35 in each group, each center treating 10 patients each.

Outcome measures

Crown failure: whether it will not be possible to place the crown because of implant failure or secondary to implant failure, or crown that has to be remade for any reason.

Implant failure: Implant failure is defined as implant mobility and/or any infection dictating implant removal, and or/any mechanical problems rendering the implant unusable. The stability of each individual implant will be measured by the independent and blinded outcome assessor manually with a reverse torque of 20 Ncm at abutment connection and at delivery of the definitive crown, or 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 ceramic.

Peri-implant marginal bone level changes: digital intraoral periapical radiographs will be made with the paralleling technique at implant placement, implant loading, 1 and 5 years after loading. In case of unreadable radiograph, the radiograph has to be made again. Radiographs will be converted to TIFF format with a 600 dpi resolution, and stored in a personal computer. Peri-implant marginal bone levels will be measured using the Scion Image (Scion Corporation, Frederick, MD, USA) software. The software will be calibrated for every single image using the known implant length or the diameter of the implant collar. 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 restorations, 1 and 5 years follow-ups, on a computer screen by an independent blinded dentist. The pictures of the vestibular and occlusal aspects have to include the 2 adjacent teeth, when present. The aesthetic evaluation will be done following the pink aesthetic score(1).

Patient satisfaction: At the delivery of the final restorations, 1 and 5 years follow-up the independent outcome assessor at each centre will ask to the patient the following questions:
1) Are you satisfied with the function of your implant supported tooth? Possible answers: yes absolutely, yes partly, not sure, not really, absolutely not.
2) Are you satisfied with the aesthetic outcome of your implant supported tooth? Possible answers: yes absolutely, yes partly, not sure, not really, absolutely not.
3) Would you undergo the same therapy again? Possible answers: “yes” or “no”.

Materials

Implant type: IB-T (ACH Medical, Gyeonggi-do, South Korea) tapered self-tapping implants, with an internal conical (11° per side) connection, a sand blasted, large grit,

acid-etched surface, and body diameters of 5.0 or 7.0 mm. Operators are free to choose implant lengths (7.0, 8.0, 9.5 and 11.0 mm) according to clinical indications.

Bone substitute: resorbable powder of non-collagenated trabecular bovine bone, having a granulometry of 0.2-1.0 mm (S1, MedPark, Busan, South Korea) and has to be hydrated with physiologic solution to become sticky.

Definitive crowns: Screw-retained zirconia 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, if they understood the scope of the study and agreed to participate. A preoperative radiograph must be obtained for every included patient.

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 analyze available bone over vital structures and adjacent to remaining natural teeth. Severe caries and periodontal disease will be identified and treated. Implant selection is predicated on the location and anatomic morphology of the proposed implant receptor site and its contiguous structures. Therefore, radiographic examinations will be performed to assist with treatment planning and used as a screening tool to assess the patient's overall dental health. To record a visual baseline, preoperative facial and occlusal digital photographs will be made of each patient intraorally to document the condition of the dental anatomy and state of soft tissue health.

OPERATIVE PROCEDURES

Please complete APPENDIX 2 (Surgical and prosthetic CRF)

Prophylactic therapy: Patients will be administered 1 g amoxicillin 3 times a day for 6 days starting the day before tooth extraction. Patients allergic to penicillin will be prescribed clindamycin 300 mg 3 times a day for 6 days starting the day before the intervention.

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 have to be carefully cleaned from any remains of granulation tissue. The wider diameter of the socket will be measured with a periodontal probe and reported in mm.

Disclosure of the randomised allocation: Once the tooth has been extracted and whether there is sufficient buccal bone, the patient will be finally included in the study and the operator will know whether the patient will receive large or conventional diameter implant by opening a sealed envelope. It is absolutely forbidden to open the envelope containing the randomisation code before. It will be reported in the Surgical and prosthetic CRF (APPENDIX 2) the patient sequential number contained in the envelope and to which group the patient was allocated.

Implant installation technique: drills will be used to prepare the implant site as suggested by the manufacturer. The intention is to stabilize the implant in the post-extractive site. Implants will be placed slightly subcrestally, about 1 to 2 mm below the most apical bone peak. The largest residual gap between the bony walls and the implant will be measured with a periodontal probe in mm. Any residual gap between the implant and the socket walls will be filled with granular bone substitute. No other grafting material is allowed.
Healing abutments will be placed and occlusal pictures showing the implants in place will be taken.
A periapical radiograph just after implant placement has to be taken.
Implants will be left to heal non-submerged for 4 months.

Post-surgical instructions and follow-up:
- Antibiotic prophylaxis previously described.
- Ibuprofen 400 mg will be prescribed, but patients will be instructed not to take it in absence of pain.
- Chlorhexidine mouthwash 0.12% for 1 minute twice a day for 2 weeks.

Check-ups
- 1 week after tooth extraction, all patients will be recalled and checked. Sutures will be removed.
- 1 month after tooth extraction all patients will be recalled and checked.

Four months after implant placement:
- Implants will be manually tested for stability.
- Impressions with pick-up or transfer-coping impression copings will be made with a polyether or a poly-vinylsiloxane material.

- Definitive screw-retained zirconia crowns (previously cemented extra-orally) will be delivered within one month.
- Periapical radiographs and clinical pictures of the study implants have to be made.
- The satisfaction questionnaire has to be filled in.

1 year after loading (APPENDIX 3):
- Crowns will be manually tested for stability.
- Periapical radiographs and clinical pictures of the study implants have to be taken.
- The satisfaction questionnaire has to be filled in.

5 years after loading (APPENDIX 3):
- Crowns will be manually tested for stability.
- Periapical radiographs and clinical pictures of the study implants have to be taken.
- The satisfaction questionnaire has to be filled in.

All patients will be recalled every 6 months for professional maintenance.

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 have to be taken and the "Complications, protocol deviation and drop-out CRF" (APPENDIX 4) should be filled in.

Time

Day 1	extraction/inclusion & allocation/implant placement/photos/rx
Week 1	post-op control
Month 1	post-op control
Month 4	implant stability/impression
Within 1 month	implant stability/definitive/rx/photos/questionnaire
1 year postloading	implant stability/rx/photos/questionnaire
5 years postloading	implant stability/rx/photos/questionnaire

Drop-outs

All drop-outs should be reported and the reason for dropping out should be investigated and reported per study group in APPENDIX 4. None of the 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 biostatistician with expertise in dentistry blinded to group allocation. A comparison of the baseline characteristics between groups will be presented. Differences in the proportion of crown/implant failures and other complications will be compared

between the groups using a chi-square test. Means of continuous variables (marginal bone level changes, aesthetic scores) will be compared using an independent sample t-test. Comparisons between, 1 and 5 years with the baseline measurements will be made by paired tests to detect any changes in marginal bone level changes for each study group with the baseline value as a covariate. All statistical comparisons will be conducted at the 0.05 level of significance.

Administrative procedures and data management

All centres are required to keep complete case report forms (CRFs) for all patients included in the study. CRFs should be filled in at the time of data collection. Complete CRFs, and memories containing the digitized clinical pictures and radiographs (radiographs can also be made on conventional films) 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 principle investigator and the responsible for data collection will have access to. Data will also be accessible to Dr Marco Esposito for monitoring and evaluation purpose at his discretion. After completion of the various follow-up points (1 and 5 years after loading) copies of al CRFs will be sent to the study coordinator, who will check the data, and store them in a computer pass-word protected. Data will be processed by an experienced statistician under supervision of the study coordinator. Patient identity will be protected and known only to the study participants listed in the present protocol.

Publication plan

1) 1 year after loading.
3) 5 years after loading.

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 4). In case of problems please contact the study coordinator without delay.

Data ownership

Data belongs to the investigators.

Clinical research forms (CRFs)

- Patient informed consent form
- Patient eligibility CRF (APPENDIX 1)
- Surgical and prosthetic CRF (APPENDIX 2)
- Follow-up CRF (APPENDIX 3)

- Complications, protocol deviation and drop-out CRF (APPENDIX 4)

REFERENCES

1. 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.