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Non-inferiority study of immediate or delayed provisionalization at posterior healed sites using NobelParallel™ CC implants

STUDY PURPOSE AND RATIONALE

Dental implants are a widely used treatment option for the replacement of lost teeth due to trauma or oral diseases. The original protocol for placement of dental implants in edentulous spaces in the maxilla or the mandible was introduced more than thirty years ago and called for a two-stage approach, i.e., surgical placement of submerged dental implants and subsequent uncovering with abutment connection, prosthesis fabrication and functional loading approximately 6 months after (Brånemark et al., 1983). Today, the time between surgery and loading in a two-stage protocol has been commonly abbreviated to 3-4 months, while immediate implant provisionalization has emerged as a reliable and predictable option in cases of adequate osseous support, having similar survival and success rates to the two-step procedure (Esposito et al., 2009). Comparison of histological healing has demonstrated no significant differences in bone to implant contact between implants surgically placed according to a two-stage protocol and those immediately provisionalized (Piattelli et al., 1993). However, Esposito et al. (2009) also noted a substantial variability among the clinical protocols used in the studies carried out so far, and concluded that additional well-designed randomized controlled trials (RCTs) are needed to fully appreciate the clinical outcomes of immediate and early loading protocols.

The design of dental implants is a subject of continuous improvement, and implant manufacturers regularly introduce new products the use of which may result in accelerated soft and hard tissue healing, increased initial implant stability, and enhanced esthetic outcomes. The purpose of this randomized, controlled trial is to compare treatment outcomes when using a newly-introduced dental implant (NobelParallel™ CC) in a one-stage or a two-stage protocol. This new implant has the same titanium oxide surface coating (TiUnite®) and the same design principles of the parallel-walled NobelSpeedy Groovy™ implants, and an internal conical connection. The implant is marketed under the premarket notifications K050406 and K073142 (510 (k), Food and Drug Administration).

SUMMARY OF STUDY PURPOSE

To compare two loading protocols using the new implant (NobelParallel™ CC) in posterior healed sites in two treatment arms: one in which the implant will be immediately provisionalized at the time of surgery, and another where the provisional crown will be delivered 3 months after the surgical procedure.

STUDY DESIGN AND STATISTICAL PROCEDURES OVERVIEW

This is a non-inferiority study of 12-month duration comparing the two treatment arms described above. Eligible patients with edentulous spaces at the maxillary or mandibular premolar/molar areas will be randomized to either an immediate provisionalization or a delayed provisionalization treatment arm. Patients in both treatment arms will receive their final fixed restoration at 4 months after surgery. The primary outcome of the study will be the radiographically assessed alveolar bone level change at the mesial and distal surface of the implant at 6 and 12 months after surgical placement. Secondary outcomes will include implant survival,

volumetric soft tissue changes, peri-implant probing depth, and implant stability by resonance frequency analysis.

POWER CALCULATIONS AND STATISTICAL ANALYSIS

Determination of sample size was based on anticipated differences in the primary outcome between the two treatment arms at 6 months (change in alveolar level from the time of implant placement). Based on similar data published in the literature (Esposito et al., 2013), we calculated with 1 mm bone remodeling in one treatment arm, and 1.5 mm bone remodeling in the second arm (i.e., expected mean difference between the two arms amounting to 0.5 mm). With a common standard deviation in both arms of 0.6 mm, the two-tailed effect size for a Student t-test (Cohen's d) amounts to 0.8333 mm. For an alpha error of 0.05 and power of 0.80, a total of 48 individuals in both arms is required for a two-tailed hypothesis. Thus, our plan is to enroll 50 individuals into the study.

Differences in the primary and secondary outcomes between the two treatment arms will be calculated using t-test for unmatched samples, after checking for data normality. Additional analyses will include regression models in which insertion torque (a measure of primary implant stability at the time of surgical placement) will be also used as a covariate along with treatment group allocation.

STUDY PROCEDURES

Eligible participants (i.e., adults ≥18 years old in need of a dental implant at a posterior maxillary or mandibular region) who have been referred for dental implant treatment at the Clinics of the College of Dental Medicine will be approached by the study investigators and the aims of the study will be explained. Signed informed consent will be obtained.

All patients will be referred for limited field cone beam computer tomography to assess presence of adequate bone volume at the area of interest, according to standard clinic protocol. Alginate impressions will be obtained to fabricate diagnostic stone casts. A vacuum-formed stent will be manufactured in the laboratory to offer fixed reference points for longitudinal probing measurements, and a radiographic stent using polyvinyl siloxane interocclusal record material will allow standardized positioning of the radiographic holder to obtain periapical radiographs with the same projection geometry.

At the day of surgery (baseline), a computer-generated sequence will assign patients to either the one-stage or the two-stage treatment arm. In both arms, the implant will be placed flush with the bone crest, after flap elevation, according to standard treatment protocol. A periapical radiograph will be obtained immediately after completion of surgery.

Patients in the one-stage group will receive a temporary acrylic crown manufactured chair-side at the same visit. Care will be taken to relieve the crown from occlusal and laterotrusive contacts. The distance from the soft tissue margin to the occlusal stent will be measured using a periodontal probe at six sites around the implant (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual) at the time of post-surgical follow-up, 1-2 weeks after surgery.

At three months after implant surgery, patients in the two-stage group will have the implant uncovered after punching the oral mucosa, according to standard protocol. An acrylic temporary crown will be delivered. Soft tissue margin assessments measurements will be carried out, as described above, will be carried out at the time of post-surgical follow-up, 1-2 weeks after surgery.

At four months after implant surgery, patients in both arms will have a final fixture level impression according to standard protocol for fabrication of the final implant supported restoration (a full contour Zirconia abutment crown with an angulated screw channel), which will be delivered approximately 2 weeks later. Resonance frequency analysis measurements will be obtained to determine implant stability using an Ostell™ device. After delivery of the final restoration, a periapical radiograph will be obtained, soft tissue margin measurements will be carried out as described above, and peri-implant probing depths will be assessed at the same six sites. An alginate impression will also be obtained to produce a stone cast to be used in volumetric measurements.

At seven months after implant surgery, patients in both treatment groups will return for a follow up visit to reinforce oral hygiene and will receive oral prophylaxis.

At twelve months after implant surgery, patients in both treatment groups will return for a follow up visit to reinforce oral hygiene and to receive oral prophylaxis. Resonance frequency analysis measurements will be obtained to determine implant stability using an Ostell™ device. A periapical radiograph will be obtained, soft tissue margin measurements will be carried out as described above, and probing depths will be assessed at the same six sites around the implant. An impression will be obtained to produce a cast to be used in volumetric measurements. The 12-month examination will conclude the study visits.

Research procedures

1. Radiographic measurements of alveolar bone level mesial and distal to the implant (at baseline, four months and 12 months) will be carried out using the MIPACS software. The implant platform will be the reference point. Note that although the measurements will be carried out for the purposes of the study, periapical radiographs after completed surgery, at the time of delivery of the final restoration, and at 12-months post-surgery are standard protocol in implant dentistry. Thus, the study does not require any additional exposure to radiation beyond what is considered the standard of care.
2. Measurements of soft tissue margin from a vacuum-formed stent at 6 sites per tooth (obtained at the day the provisional crown is delivered, i.e. at the post-operative visit 1-2 weeks after implant placement in the one-stage treatment arm, or at the post-operative visit 1-2 weeks after implant uncovering in the two-stage arm).
3. Probing depth measurements around the implant (at 4 and 12 months).
4. Volumetric assessments, based on digitally super-imposed casts (obtained at screening, 4 months and 12 months).
5. Resonance frequency analysis measurements using a Ostell™ device (at 4 and 12 months). These are non-invasive measurements of implant stability.

STUDY DRUGS
N/A

STUDY INSTRUMENTS
The NobelParallel™ CC implant is a new implant that has the same titanium oxide surface coating (TiUnite®) and a parallel-wall body design similar to the NobelSpeedy groovy™ and a conical internal connection. Both the implant and its prosthetic components have regulatory clearance [510(k)] by the Food and Drug Administration.

ADDITIONAL DATA COLLECTION
We will collect and review standard medical and dental history forms to confirm eligibility (age 18 years or older, participants who are systemically healthy or have controlled common systemic conditions, not pregnant, non-smoking or smoking <10 cigarettes/day, have no parafunctions or excessive occlusal forces, are not currently under orthodontic therapy, and have a stable occlusion). Intraoral photographs will be obtained for documentation purposes.

STUDY SUBJECTS
We will recruit 50 subjects among those referred to the College of Dental Medicine for tooth replacement using a dental implant in a posterior maxillary or mandibular region (premolar/molar area).

ADDITIONAL INCLUSION CRITERIA
Age 18 or older
Healed extraction sockets (extraction carried out at least 3 months prior to recruitment)
Implant site free of infection
Systemically healthy patients or with controlled common systemic conditions
Adjacent teeth present both mesially and distally to the implant site

EXCLUSION CRITERIA
Pregnancy or intent to be pregnant over the next 12 months
Current smoking exceeding 10 cigarettes/day
Parafunctional habits/ excessive occlusal forces
Current orthodontic therapy
Uncontrolled hypertension (blood pressure over 160/100) or poorly-controlled diabetes (HbA1c>8%).

RECRUITMENT
Potential participants will be approached by the study investigators and the scope and the procedures of the study will be thoroughly explained. Eligible individuals willing to participate will provide informed consent.

CONFIDENTIALITY OF THE DATA

Participants will be assigned individual study numbers that will be used to link all collected study data. All endpoint devices used for data collection will be password-protected and encrypted. PHI/PII data and all other study data will be stored in a secure, certified database. The following individuals/ institutions/ representatives will have access to the records: the Principal Investigator and co-investigators, the FDA, the Department of Human Health and Human Services, the Columbia University/New York Presbyterian Hospital, and the Institutional Review Board. Absolute confidentiality cannot be guaranteed because of potential need to share this information with the above parties. Only aggregate findings of this study will be published.

POTENTIAL CONFLICT OF INTEREST

The study is an investigator-initiated randomized controlled trial, where the Principal Investigator serves as the Sponsor-Investigator. The study is partially supported by a grant provided by the implant manufacturer (Nobel Biocare). None of the investigators have any financial interest in the company or have served as paid consultants.

LOCATION OF THE STUDY

All study procedures will take place at the Clinics for Post-doctoral Periodontics and Post-doctoral Prosthodontics, College of Dental Medicine, Columbia University Medical Center, Vanderbilt Clinic, 9th floor.

POTENTIAL RISKS

Study related risks: The overall success of dental implants exceeds 95%. Risks associated with the study are identical to those associated with surgical implant placement and include soreness, discomfort, pain, infection, nerve damage and implant failure.

Protection against risks: Implants will be placed and restored by post-doctoral residents who are proficient in the surgical and restorative aspects of implant dentistry, under faculty supervision. Patients will receive post-operative antibiotic and analgesic coverage, according to standard clinical protocol.

POTENTIAL BENEFITS

Patients will have the costs associated with implant surgery and provisional restoration waived, as these will be covered by funds provided by the implant manufacturer (NobelBiocare).

ALTERNATIVE THERAPIES

1) not to replace the missing tooth
2) to receive a removable partial denture to replace the missing tooth
3) to receive fixed bridge to replace the missing tooth
4) to receive implant therapy and restoration outside the study

COST TO SUBJECTS

Patients will need to pay for the final/permanent restoration (implant-supported crown). The costs associated with implant surgery and provisionalization will be waived.

MINORS AS RESEARCH SUBJECTS

No minors will be included in the study, as dental implants are not a therapeutic option in individuals with ongoing skeletal growth.

RADIATION OR RADIOACTIVE SUBSTANCES

The radiographs obtained as part of this protocol are those required by the standard of care in implant dentistry. The study does not involve any additional exposure to radiation solely for research purposes.

REFERENCES

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