September 26th 2021

Study Protocol and Statistical Analysis Plan

ClinicalTrials.gov Identifier: NCT04243421

Marginal Bone and Soft Tissue Alterations After Use of OsseoSpeed EV Profile Implants

Aim
Evaluation of the marginal bone and soft tissue alterations after the OsseoSpeed™ EV Profile implants placement in anterior maxilla.

Study design
A case series study. Each patient will provide only one site with sloped ridge for implantation. The trial will have a duration of 1 year.

The principles outlined in the Declaration of Helsinki on clinical research involving human subjects will be adhered to a written informed consent which will be obtained for each patient.

Inclusion criteria

- lack of tooth in position of central incisors, canines and premolars
- minimum age – 18 years

The definitive inclusion of the site will be made at surgery after final osteotomy - if the site demonstrates a lingual-buccal bone height discrepancy of 1.5-2.0 mm.

Exclusion criteria

- Smoking
- Uncontrolled diabetes
- Pregnancy or lactation
- Poor oral hygiene

Number of patients to be included

It is planned to include 30 patients in to the study.

Outcome measures

Implant survival: the reason for implant loss will be recorded.

Complications and adverse events: any complication (flap dehiscence, suppuration, etc.) and adverse events will be recorded and reported by study group by the blinded assessors.

Pink esthetic score (1) – at the temporary crown delivery, at final crown delivery, 6 months post final crown delivery
Papilla index (2) - at the temporary crown delivery, at final crown delivery, 6 months post final crown delivery

Changes in radiographic marginal bone levels and width at buccal and palatal aspects: differences between baseline (the day of surgery) and 1-year measurements on CBCT will be made.

Materials

- Implant OsseoSpeed™ EV Profile ⌀4.2 mm
- cover screw
- healing abutment
- temporary abutment
- temporary crown
- impression coping
- implant replica
- Atlantis abutment
- definitive full ceramic crown
- Sutures: non-resorbable 5/0 or 6.0 Ethilon (Ethicon Johnson & Johnson Company, New Brunsvick, NJ, USA)

Clinical procedures

Screening visit
Potentially eligible patients are screened to establish their eligibility for the study.

Prior to enrollment, all patients will be asked 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), will be allowed to ask questions pertaining to this study, and will be informed of treatment alternatives. The study is open to qualifying patients without regard to sex or race.

Once identified one or more eligible sites, only one site will be included and treated in the study for each patient: the site demonstrating a lingual-buccal bone height discrepancy of 2.0-3.0 mm visible in CBCT. Preoperative CBCT have to be taken to screen the patient as potentially eligible for being included in the trial.

The definitive inclusion of the site will be made at surgery stage, after final osteotomy – if there will be a lingual-buccal bone height discrepancy of 1.5-2.0 mm measured with a periodontal probe PCP-15 (Hu-Friedy, Leimen, Germany).

Prophylactic procedures: 1 g of Amoxicillin will be taken twice a day starting one hour before the surgical intervention up to the fifth day after surgery. Patients allergic to penicillin will be prescribed 600 mg Clindamycin to be taken twice a day starting one hour before the surgical

intervention up to the fifth day after surgery. Patients will rinse with chlorhexidine mouthwash 0.2% for 1 minute prior to the intervention.

Intraoral facial digital photographs will be made of each potentially eligible site to document the condition of state of soft tissue health. Baseline CBCT have to be taken immediately after surgery.

Surgical procedures

Local anaesthesia – Articain (Ubistesin forte, 3M ESPE, Germany).

Flap will be designed following the crestal and releasing incisions (if necessary). All granulation tissue will be removed and the roots of neighboring teeth will be carefully debrided with hand and/or mechanical instruments. Bone re-contouring is not allowed.

After having completed the cleaning, the surgeon will perform the osteotomy. After the use of the final drill ⌀3.2 the surgeon will take the measurement of the buccal and palatal/lingual walls height.
If wall discrepancy is 1.5-2mm the site will be included in the study.
Clinical photographs of probe into the osteotomy have to be taken.
The osteotomy will be prepared with the conical drill therefore the implant will be placed in special manner - it's sloped part is located at the buccal osteotomy preparation. The buccal rim of the implant is positioned at the crestal bone level, the palatal rim may be situated either at the level of the bone crest or 0.5 mm below.
The flap will be sutured with 5/0 or 6/0 non-absorbable Ethilon sutures using the mattress and single interrupted sutures. Clinical photographs of the treated site after flap suturing have to be taken.

Post-surgical instructions and follow-up

- Ibuprofen 400 mg 2-4 times per day will be prescribed in case of pain. In case of gastric problems it will be replaced by Paracetamol 1 g (max 4 g per day).
- Patient will be reminded to go on with the antibiotic prophylactic therapy as previously described.
- Chlorhexidine mouthwash 0.12% for 1 minute twice a day for 3 weeks will be provided.
- Suture removal after 2 weeks.

Check-ups and maintenance
Appointments will be scheduled at weeks 1, 2, 4, and 6. Clinical photographs will be taken. At these time points presence of suppuration and flap dehiscence will be recorded dichotomously as presence/absence.

Uncovering procedure will be scheduled at 8 weeks post-op. After crestal incision and gentle flap elevation the height of denudated buccal implant surface (if present) will be measured using a periodontal probe. Then the hilling abutment will be screwed in and single interrupted sutures

will be placed with the use 5/0 or 6/0 non-absorbable Ethilon sutures (if necessary). Suture removal is planned 7 days after procedure. Clinical photographs will be taken.

Temporary crown will be delivered 3 months post implant placement. Clinical examination (PES, PI) will be performed. Clinical photographs will be taken. Control CBCT will be taken.

Final prosthetic reconstruction will be delivered 6 months post-op. Clinical examination (PES, PI) will be performed. Clinical photographs will be taken.

1 year evaluation
Clinical examination (PES, PI) will be performed.
Clinical photographs of the study site have to be taken.
Control CBCT will be taken.

In case of any complication observed during any of the scheduled visit or during an emergency visit, intraoral radiographs and clinical photographs have to be taken and the CRF should be filled in.

Summary of the procedures and follow-up

Day 0	Antibiotic coverage, preoperative clinical photographs, flap, intrasurgical measurements with definitive inclusion, treatment, post-operative photographs, CBCT
Week 1	Check: suppuration, dehiscence
Week 2	Check: suture removal, suppuration, dehiscence, photographs
Week 4	Check: suppuration, dehiscence, photographs
Week 6	Check: suppuration, dehiscence, photographs
Week 8	Uncovering procedure, intrasurgical measurements, healing abutment installation, photographs
Month 3	Temporary prosthetic reconstruction delivery, PES, PI, photographs, CBCT
Month 6	Definitive prosthetic reconstruction delivery, PES, PI, photographs
1 year	PES, PI, photographs, CBCT.

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
The variables will be described by the parameters of descriptive statistics, i.e. arithmetic mean with 95% confidence interval, standard deviation, median, lower and upper quartile, as well as the minimum and maximum value.
The normality of the distribution will be tested with the Shapiro-Wilk test.
For the comparisons of 2 groups, the Student's t-test for related variables or Wilcoxon's test will be used (depending on whether the assumption of normal distribution is met).
Related variables ANOVA or Friedman's test along with Dunn's multiple comparison test with Bonferroni correction will be used to compare the 3 groups (depending on whether the assumption of normal distribution is met). Additionally, the trend analysis will be performed with the Page test or the linear trend test.
The results were considered statistically significant at $p<0.05$.

PQStat version 1.8.0.392 will be used for statistical analyzes.

Administrative procedures and data management

Clinical record forms (CRFs) should be filled in at the time of data collection. Complete CRFs, and disks containing the digitized clinical photographs 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 principle investigator and the responsible for data collection will have access to. 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 "Protocol deviation and drop-out CRF"

Publication plan

One publication is planned to be submitted to scientific journal on the field of oral implantology.

References

1. Belser UC, Grutter L, Vailati F, Bornstein MM, Weber H-P, Buser D. Outcome Evaluation of early placed maxillary anterior single-tooth implants using objective esthetic criteria: A cross-sectional, retrospective study in 45 patients with a 2- to 4-year follow-up using pink and white esthetic scores. J Periodontol 2009; 80:140-151.
2. Jemt T. Regeneration of gingival papillae after single-implant treatment. Int J Periodontics Restorative Dent 1997; 17: 326-333.