Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine

Clinical Research Protocol

Project Name:	Effect of different suture techniques on early healing of peri-implant soft tissue following open-flap implant surgery in esthetic area: a randomized clinical trial comparing horizontal and vertical mattress sutures
Version Number:	V 1.0
Version Date:	2021/10/20
Project Manager:	
Start and End Dates:	2021/12 – 2022/12

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Researcher's Statement and Protocol Signature Page

As the main person in charge of this research project, I will follow the Measures for Ethical Review of Biomedical Research Involving Human Subjects (2016), WMA Declaration of Helsinki (2013), CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) and the ethical principles of the GCP. Under the guidance of drug clinical trial quality management regulations, I will conduct research in accordance with the requirements of this protocol approved by the ethics committee to ensure the scientific nature of the research and protect the health and rights of the subjects.

Name: __Prof. Maurizio Tonetti_
Signature:

Date:

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1. Protocol Abstract

Project Name		Effect of horizontal and vertical mattress sutures on early healing following open-flap implant surgery in esthetic area: a randomized clinical trial				
Version Number		1.0	Version Date		2021-10-20	
Apply and Participating Units		Shanghai Ninth People's Hospital				
Research Nature		Randomized clinical trial	Sample Size		20	
Research Purposes		To compare the blood perfusion and early healing of horizontal mattress suture with vertical mattress sutures following open-flap implant surgery.				
Participants		Patients want single implant replacement in esthetic area				
Research Methods		A randomized, open-label, controlled clinical trial Noninvasive procedures will be used to assess the primary and secondary outcomes.				
Inclusion Criteria		With sufficient bone width (⩾6mm), With mesial-distal distance over 8mm, age over 18, Willing to participate				
Exclusion Criteria		Patients want multiple adjacent implant replacements in esthetic area, Untreated periodontitis, Smokers, Diabetes mellitus				
Research Progress Plan		The study is expected to last for 3 months including 1 months follow-up period after implant surgery				
Statistics Analytical Methods		Descriptive statistics and inferential statistics performed in SPSS software, version 26.0				
Publication Form of Research Results		Publication in international specialty Journal				
Main Researcher		Maurizio S. Tonetti	Title	Chair Professor	Date of Birth	18 May 1961
Major Members of the Project	Name	Date of Birth	Title	With or Without GCP Certificate	Responsibility	
	Prof. Lai Hongchang		Professor	With GCP	Co-investigator	
	Dr. Junyu Shi		Doctor	With GCP	Co-investigator	
	Dr. Deng Ke	07 Oct 1991	Doctor	With GCP	Co-investigator/ study coordinator	
	Dr. Shujiao Qian		Doctor	With GCP	Co-investigator	
	Dr. Beilei Liu		Doctor	With GCP	Co-investigator/ study coordinator	
	Dr. Xiao Zhang		Doctor	With GCP	Statistician	

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2. Research Background

Dental implant placement is a highly technique-sensitive procedure. Proper wound closure and stabilization of wound margins in a desired position are critical events that influence the success of the outcomes, particularly in more demanding surgeries such as esthetic and reconstructive surgery.

Wound healing primarily depends on early formation of the blood clot and the establishment of an attachment of the clot that is resistant to mechanical forces acting on the flap and opposing surfaces participating in the wound closure. Suture is the major area of concern in situations where mechanical stability of the flap is required. Ideally, surgical suture should hold edges in apposition until the wound has healed. Various types of sutures have been proposed to stabilize and secure the surgical flap to promote the optimal healing.

For a wound that is deeper in nature, a mattress stitch can be placed, providing better strength. The deeper penetration into the soft tissue layers minimizes tension and allowing for better closure at the wound edges. Mattress sutures can be applied as vertical or horizontal subtypes. According to a previous studies, mean maximum pulling force in a standardized model was 5.69 N (SD, 0.88), 7.25 N (SD, 1.33) and 8.11 N (SD, 1.00) for single interrupted suture, vertical and horizontal mattress suture, respectively. In addition, the blood supply after implant surgery mainly comes from the apex aspect due to the disruption of periosteal blood supply. Thus, the amount and direction of tension of the different subtypes of mattress sutures can have a significant impact on the blood supply after implant surgery.

So far, various studies have compared the effect of horizontal mattress suture (HMS) with vertical mattress suture (VMS) on wound healing in different wound. A 1-year clinical study compared the early healing following HMS with VMS after pancreaticogastrostomy. The result showed that HMS was superior to VMS for preventing early postoperative complications and did not affect pancreatic function. Another study evaluated the medical stitch in trans-osseous-equivalent rotator cuff repair. The results showed that VMS failed at higher loads compared with HMS (568.9 ± 140.3 vs 451.1 ± 174.3 N; P = 0.025).

Laser Doppler flowmetry (LDF) is used to measure the tissue blood perfusion noninvasively and has been widely used in the field of plastic surgery. It can detect circulatory disturbances at early stages and predict surgical complications.

However, limited studies have evaluated the effect of the subtype of mattress sutures on the early wound healing and microcirculation changes of peri-implant soft tissues following implant

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surgery using LDF. Therefore, it is important to understand the effect of different suture techniques on early wound healing following implant surgery.

3. Study Objectives

The overall aim of this study is to compare the microcirculation changes of peri-implant soft tissues following open-flap implant surgery using different suture techniques. The study also aims to monitor healing dynamics by means of observing volumetric alterations of the peri-implant soft tissues following implant placement.

3.1 Primary Objective

To compare the peri-implant blood perfusion volume responses during healing with horizontal mattress suture and vertical mattress sutures following open-flap implant surgery.

3.2 Secondary Objective

To compare the peri-implant blood oxygen saturation, blood flow velocity and haemoglobin count during healing with horizontal mattress suture and vertical mattress sutures following open-flap implant surgery.

3.3 Additional Objective

To compare three-dimensional soft-tissue volumetric changes, wound healing score and patient-related outcomes (visual analogue scale) during healing with horizontal mattress suture and vertical mattress sutures following open-flap implant surgery.

4. Study Hypothesis

The effect of the different pressure directions of horizontal and vertical mattress sutures on the soft tissue blood supply can be detected by laser Doppler flowmetry.

5. Study Methods

5.1 Overall Design of the Study

This will be a parallel group, single‐centred, open-label, adaptive-design clinical trial with balanced randomization.

5.2 Sample Size

Null hypothesis is that no significant difference of blood perfusion volume change (PU) can be found at each time points between two groups. Alterative hypothesis is Significant difference of blood perfusion volume change (PU) can be found at least one time point between two groups.

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Because actual difference of primary outcome between two groups may vary. An adaptive design is adopted to adjust planned sample size, type of comparison according to actual statistics calculated from 20 subjects. If the revised sample size is within the planned sample size then the planned sample size is not to be adjusted. If the revised sample size is larger than planned sample size then the revised sample size will be considered. The study population, intervention and primary outcome will stay the same throughout this study.

5.3 Randomization and Concealment

The patients will be randomized to one of the two groups: vertical mattress suture (test group) and horizontal mattress suture (control group) on a 1:1 ratio. Randomization will be performed by computer generated random codes. Allocation will be concealed to the surgeon until completion of all surgical steps except for suturing by opaque envelopes.

5.4 Blinding

As it is not possible to blind the therapist and examiner for the suture, an open-label design will be used in this study

6. The Selection, Withdrawal and Management of Subjects

6.1 Inclusion Criteria

Consecutive patients fulfilling the following inclusion criteria will be invited to participate in the study:

- Aged 18 and above
- Subjects want single implant treatment in esthetic area (premolar to premolar) in maxilla
- With sufficient bone width (⩾6mm)
- With mesial-distal distance over 8mm
- Evidence of subject ability to achieve good oral hygiene and control periodontitis in the whole of the dentition (FMPS<20% and FMBS<20%)
- Ability to understand study procedures and to comply with them for the entire length of the study. Ability and willingness to give written informed consent.

6.2 Exclusion Criteria

All candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- Subjects want multiple adjacent implant treatment
- Patients with inadequate bone volume where major bone augmentation would be required at implant location.

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- Subjects with untreated periodontitis
- Current smokers
- Subjects with diabetes mellitus.
- Pregnant females
- Participation in another intervention trial
- Inability or unwillingness of individual to give written informed consent.

6.3 Management of Subjects

(1) Study Enrollment Procedures

Consecutive subjects will be screened for eligibility in the Department of Implant Dentistry of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Potentially eligible patients will be provided information about the study objectives by one of the investigators and full informed consent will be sought from potentially interested subjects.

(2) Informed Consent Process

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Documental consent form will be provided to patient, with verbal explanation by one of the investigators. The procedure would be done at the beginning of the study after verification of inclusion and exclusion criteria.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the investigators to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the investigator who presented and obtained the informed consent. A copy of the signed informed consent will be given to the participants. The original signed form will be retained at the study site.

7. Study Procedures

7.1 Treatment of Trial Participants

7.1.1 Control of periodontitis (if needed)

Standard periodontal treatment needs to be completed in the dentition before the patient can be

enrolled into the study. The patient needs to show evidence of good oral hygiene (FMPS<20%) and control of bleeding on probing (FMBS<20%).

7.1.2 Surgical procedures

One experienced specialist in Implant Dentistry will perform the implant surgeries for all patients. Surgery will be standardized, and the same procedures/materials will be employed to ensure consistency.

- Local anesthesia will be performed by infiltration at the buccal vestibular sulcus and the palatal side of the alveolar ridge.
- Following anesthesia, a mid-crestal ridge incision will be started and continue with sulcular incisions around both adjacent teeth to the implant bed using blades #.11 or No.12.
- A full-thickness mucoperiosteal flap will be raised and soft tissue remnants will be removed to fully expose the alveolar ridge.
- A standardized dental implant (Nobel Active) will be placed according to the manufacturer's instructions. Cover screws will be used.
- Different suture techniques will be used according to the group allocation to achieve wound closure after opening the envelope.
- The sutures will be removed after 7 days.

7.1.3 Post-surgical instruction

- Post-operative pain and oedema will be controlled with analgesics (Ibuprofen, TSKF, 600mg, 2 times, interval 6-8 hours). Antibiotic regimen will also be performed (amoxicillin, Xinya Co, 2g, 60 minutes before surgery).
- Rinsing with 0.12% chlorhexidine will be prescribed 3 times/day for the first 2 weeks
- Another single clinician, blind with respect to the group assignment, will perform all measurements.

7.2 Handing of study interventions

Allocation will be concealed to the surgeon until completion of all surgical steps except for suturing. Thereafter, vertical mattress sutures (test group) or horizontal mattress sutures (control group) will be performed according to the group allocation to achieve wound closure after opening the envelope.

(1) Control group

In the control group, the participants will receive the following sutures to achieve wound closure:

- One mesial single interrupted suture (1 mm from the mesial teeth, 2-3mm from needle-in points to the incision)
- One distal single interrupted suture (1mm from the distal teeth, 2-3mm from needle-in points to the incision)
- One horizontal mattress suture (5-6mm from needle-in points to the incision, 3-4mm from needle-in to needle-out points)

(2) Test group

In the test group, the participants will receive the following sutures to achieve wound closure:

- One mesial single interrupted suture (1mm from the mesial teeth, 2-3mm from needle-in points to the incision)
- One distal single interrupted suture (1mm from the distal teeth, 2-3mm from needle-in points to the incision)
- One mesial and one distal vertical mattress sutures (5-6mm from needle-in points to the incision which are in keratinized tissues, 2-3mm from needle-out points to the incision, 3-4 mm from mesial and distal sutures)

7.3 Course of Treatment and Visit Points

7.3.1 Screening and Enrollment

Screening evaluations for this study will be performed in the Department of Implant Dentistry of Shanghai Ninth People's Hospital. Clinical and radiographic assessment will be performed for treatment plan. Subjects fulfilling the inclusion and exclusion criteria will be invited to participate in the study and receive an explanation of the study, its objectives, benefits and risks by the investigator in the context of informed consent. The following information will be collected and recorded after the inclusion of the participants.

(a) Demographics

The date of birth, gender and drinking habits will be recorded.

(b) Medical History

Details of medical, including diabetes mellitus, cardiovascular diseases and other systemic diseases will be recorded.

(c) Concomitant Medication

All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs.

7.3.3 Baseline Assessments (presurgical measurements T0)

Baseline assessment will be performed by another trained clinician, blind with respect to the group assignment, including:

(1) Clinical photographs

(2) Clinical measurements including:

- The full-mouth plaque score (FMPS), full mouth bleeding score (FMBS)
- Probing pocket depth (PPD) and clinical attachment level (CAL) for the two adjacent teeth to the treatment site
- Amount of keratinized tissue (KT) measured on the mid buccal of the treatment site

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(3) Intra-oral scanning

Intraoral digital impressions of the alveolar ridge, buccal/palatal soft tissues and at least two adjacent teeth will be conducted using an intraoral scanner (3Shape trios 3,) by a single trained and calibrated examiner. The digitized 3D impressions will be saved and exported in the Standard Tessellation Language (STL) file format.

(4) Tissue perfusion assessment (LEA measurements)

A laser Doppler flowmetry machine (LDF) (LW1111, LEA) will be used to measure the tissue perfusion. The machine can provide the following 4 types of measurements: 1) blood perfusion volume, 2) blood flow velocity, 3) haemoglobin count, 4) blood oxygen saturation. The diameter of the measurement probe will be 3mm. Two surgical stents with 6 measurement holes will be fabricated to ensure the measurement are repeatable. The small hole with the same diameter of the LDF probe will be created on the buccal and palatal sides of the incisions. LDF probe will be held at a standardized position perpendicular to the tissue and at a distance of 0.5-1 mm from the gingiva and remain fixed during repetitive LDF measurements.

The recordings of the probe of the LDF will be made through holes. The followin64 region of interests (ROIs) will be measured: 1) central buccal: the area in the central of buccal aspect, 2) central palatal: the area in the central of palatal aspect, 3) mesial buccal: the area in the buccal aspect and 2.5mm from the mesial tooth, 4) distal buccal: the area in the buccal aspect and 2.5mm from the distal tooth, 5) mesial palatal: the area in the palatal aspect and 2.5mm from the mesial tooth, 6) distal palatal: the area in the palatal aspect and 2.5mm from the distal tooth.

The LDF measurements at the test and control group will be performed on the day of the surgery before the injection of the local anaesthesia (baseline), 1min following local anaesthesia induction, immediately following completion of the surgical procedure, post-operative hours 1,2,6 and on post- operative days 1, 3, 7, 14, 30.

(5) Suture tension (Flap Tension Meter)

Immediately after suture, the tension exerted on the flap margins with the respective sutures was measured using a highly sensitive electronic tension/pressure device (Flap Tension Meters, Imedico GmbH, Zurich ZH, Switzerland). Tension was read to an accuracy of 0.001N (0.1 g).

7.3.4 Follow-up Visits and evaluation

Follow-up assessment will be performed by the same trained clinician, blind with respect to the group assignment, additional assessments including:

(1) Soft tissue thickness

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The thickness of the soft tissue will be performed with calipers 2 mm from incision margin in both buccal and palatal side.

(2) Clinical wound healing assessment

EHI index will be used for clinical wound healing assessment: a) complete flap closure – no fibrin line in the interproximal area; b) complete flap closure – fine fibrin line in the interproximal area; c) complete flap closure – fibrin clot in the interproximal area; d) incomplete flap closure – partial necrosis of the interproximal tissue; e) incomplete flap closure – complete necrosis of the interproximal tissue.

(3) Patient-reported outcomes

Visual analogue scale (0-10) will be used to evaluate the post-operative pain.

Immediate after anesthesia – T1

- LEA measurement
- Soft tissue thickness (after flap elevation)

Immediate after suture – T2

- LEA measurement
- Intra-oral scanning
- Suture tension
- PROMs

1 hour after surgery – T3

- LEA measurement
- Intra-oral scanning

2 hours after surgery – T4

- LEA measurement
- Intra-oral scanning

6 hours after surgery – T5

- LEA measurement
- Intra-oral scanning
- PROMs

24 hours after surgery – T6

- LEA measurement
- Intra-oral scanning
- Clinical wound healing assessment
- PROMs

72 hours after surgery – T7

- LEA measurement

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- Intra-oral scanning
- Clinical wound healing assessment
- PROMs

7 days after surgery – T8

- LEA measurement
- Intra-oral scanning
- Suture removal
- Clinical wound healing assessment
- PROMs

14 days after surgery – T9

- LEA measurement
- Intra-oral scanning
- Clinical wound healing assessment

30 days after surgery – T10

- LEA measurement
- Intra-oral scanning
- Clinical wound healing assessment

8. Outcomes and evaluations

8.1 Outcomes

8.1.1 Primary outcomes

- Blood perfusion volume (PU) change during the observation period

8.1.2 Secondary outcomes

- Blood flow velocity change during the observation period
- Hemoglobin count change during the observation period
- Blood oxygen saturation change during the observation period
- Three-dimensional soft-tissue volumetric changes during the observation period
- Changes in clinical wound healing score during the observation period
- PROMs (VAS)

9. Safety Evaluation

9.1 Adverse Events

The collective evidence from numerous clinical trials reveals consistent findings that implant surgery is a safe and the most effective approach for missing tooth replacement. No adverse events

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have been reported. Sometimes implant failure happens, but a second implant placement can be performed after healing.

9.2 Follow-up for Adverse Events

Adverse events (AE), if any, will be managed according to current standard of care for the specific condition. The principal investigators will assess and manage the condition to the best of his knowledge and refer to specialist care if appropriate and in the best interest of the participant. AE will be considered resolved once the principal investigators concur that to be the case.

10. Data Quality Assurance

10.1 Quality Control and Assurance

10.1.1 Training and Calibration

All investigators involved in this study will be trained appropriately for the standard operating procedures including the implant surgery and measurements

- The examiner will be trained and calibrated with the LEA measurements and intra-oral scanning before the start of the study.
- The therapist, who will deliver the implant surgery, will be an experienced specialist in implant dentistry fulfilling the Shanghai requirements.
- The investigator who performs interventions for the test/control groups will be trained in a standardized session including the spacing of the mattress sutures and tension of the knotting.

10.1.2 Protocol Deviations

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Protocol deviations will be assessed during regular monitoring.

10.1.3 Regular Monitoring

Regular monitoring for assuring protocol compliance, and data quality at the clinical site, including review of source documents and records, consent forms, etc will be performed by an investigator trained in both GCP and the specific procedures. Furthermore, the clinical research coordinator will audit the case report forms for the first few patients to ensure correct filling of forms. The study will also be monitored by the compliance office of the National Clinical Research Center of Oral Diseases and Clinical Research Center of the 9th People Hospital.

10.1.4 Record Keeping

All investigators are required to keep complete clinical records, clinical samples, study data for all the patients included in the study. Radiographs and intraoral scanning images should be archived

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in digital format and stored securely both as part of the patient clinical record and as part of the study records. The study coordinator will collect a copy of all digital files. All research-related records will be retained for at least 5 years after study completion.

10.1.5 Patient Scheduling

In order to improve compliance with protocol, all subjects participating in the study will have an alert in their patient record identifying them as participant to this protocol in order to alert administrative staff on the need to follow a stringent timing of follow-up appointments.

10.1.6 Investigator assistance

Investigators can contact the principal investigators for any question, doubt or problem that could emerge. For clinical, protocol, patient care and adverse event reporting, investigators should contact Dr. Shi at the following numbers:

Dr. Shi Tel 13636340883

10.2 Data Management

(1) Overview of Data Management Methods

- Primary data will be stored and retrieved from the Shanghai Ninth People Hospital. The participants will be identified by a study specific participant number and/or code in the secondary database after retrieving data from primary database for data analysis. CRF will be in written format with identifiers removed and assigned with identifying codes. Codes will be stored safely and separated from data. The name and any other identifying detail will NOT be included in any secondary study data electronic file. All documents will be stored securely and only accessible by trial staff and authorized personnel.
- The investigators will archive source documents for each patient entered in the study, signed and witnessed informed consent forms, patient questionnaires. Furthermore, the investigators will maintain a study patient list that will allow matching Case Reports with source documents, a screening log, the investigator manual, digital radiographs, intraoral scanning images and clinical samples.

(2) Internal Analysis Plan of Data

N/A

(3) The Frequency of Data Security and Monitoring Reports Submitted to the Ethics Committee

Given the low risk profile of the study, data safety and monitoring reports will be submitted to the Ethics committee every 6 months.

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11. Statistical Analysis

11.1 Statistical Software and General Requirements

Data analysis will be performed in SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance will be set at 0.01 for all tests.

11.2 Statistical analysis plan

(1) Descriptive statistics will be run to describe the demographic, clinical and biological characteristics of the study population. Means with standard deviations (SD) or medians with interquartile range (IQR) will be used to describe continuous variables. Frequencies will be used to describe categorical variables.

(2) The normality of clinical and biological parameters at baseline and each re-evaluation visit will be tested for normality using the Kolmogorov-Smirnov test. The homogeneity of the clinical and biological parameters at baseline and each re-evaluation visit will be tested using Levene's test.

(3) The differences over time within groups for data will be analyzed with the non-parametric Wilcoxon's Signed Ranks tests or Paired t-tests according to the data normality and homogeneity.

(4) The comparison of parameters between the control and the test group at baseline and each re-evaluation visit will be performed with the Mann–Whitney U test or Student t test according to the data normality and homogeneity, respectively.

12. Ethics Requirements and Informed Consent

The Investigators will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2013). The Investigators will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6 (R1) July 1996. The protocol, informed consent form and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) for written approval. A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. The trial staff will ensure that the participants' anonymity is maintained.

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