Minimally-invasive Non-surgical Vs. Surgical Approach for Periodontal Intrabony Defects: a Randomised Controlled Trial

CURRENT STATUS: ACCEPTED

Luigi Nibali  l.nibali@qmul.ac.uk
Queen Mary University of London School of Engineering and Materials Science
Corresponding Author
ORCiD: 0000-0002-7750-5010

Vasiliki Koidou
Queen Mary University of London

Simona Salomone
Queen Mary University of London

Thomas Hamborg
Queen Mary University of London

R Allaker
Queen Mary University of London

Rinat Ezra
Queen Mary University of London

Lifong Zou
Queen Mary University of London

Georgios Tsakos
University College London

Nikos Gkranias
Queen Mary University of London

Nikos Donos
Queen Mary University of London

DOI:
10.21203/rs.2.263/v2

SUBJECT AREAS
General Medicine
KEYWORDS
Periodontitis, intrabony defect, minimally-invasive, quality of life, bone
Abstract

Background

Periodontal intrabony defects are usually treated surgically with the aim to increase attachment and bone levels and reduce risk of progression. However, recent studies have suggested that a minimally-invasive non-surgical therapy (MINST) leads to considerable clinical and radiographic defect depth reductions in intrabony defects. The aim of this study is to compare the efficacy of a modified MINST approach with a surgical approach (modified minimally-invasive surgical therapy, M-MIST) for the treatment of intrabony defects.

Methods

This is a parallel-group single-centre examiner-blind non-inferiority randomised controlled trial with a sample size of 66 patients. Inclusion criteria are age 25-70, diagnosis of periodontitis stage III or IV (grades A to C), presence of ≥1 ‘intrabony defect’ with probing pocket depth (PPD) >5 mm and intrabony defect depth ≥3mm. Smokers and patients who received previous periodontal treatment to the study site within the last 12 months will be excluded. Patients will be randomly assigned to either the modified MINST or the M-MIST protocol and will be assessed up to 15 months following initial therapy. The primary outcome of the study is radiographic intrabony defect depth change at 15 months follow-up. Secondary outcomes are PPD and clinical attachment loss (CAL) change, inflammatory markers and growth factors in gingival crevicular fluid, bacterial detection, gingival inflammation and healing (as measured by geometric/thermal camera imaging in a subset of 10 test and 10 control patients) and patient-reported outcomes.

Discussion

This study will produce evidence about the clinical efficacy and potential applicability of a modified MINST protocol for the treatment of periodontal intrabony defects, as a less
invasive alternative to the use of surgical procedures.

Background

Periodontal diseases are inflammatory conditions that affect the supporting apparatus of the teeth. Periodontitis and its non-destructive partner condition, gingivitis, are collectively one of the most prevalent inflammatory conditions of humanity [1]. In 2010, severe periodontitis was estimated to be the sixth most prevalent disease in the world, with a prevalence of 11.2%, gradually increasing with age [1]. In periodontitis, the presence of subgingival plaque biofilms in susceptible individuals determines an inflammatory reaction, leading to loss of the supporting connective tissue and alveolar bone. Periodontitis is now classified into different stages (I to IV) based on disease severity and into grades (A to C), based on risk of progression [2]. Periodontal osseous destruction can result in horizontal or vertical bony defects, depending on the direction and extent of the apical propagation of the plaque-induced lesion [3]. The treatment of periodontitis involves a non-specific reduction of the bacterial load below the gingival margin [4], which can be achieved by oral hygiene instructions and non-surgical periodontal therapy (NSPT). More advanced cases need surgical treatment or extractions. The overall objective of the treatment is the elimination of periodontal inflammation through disruption of the subgingival biofilm, with reduction of gingival PPD and CAL, resulting in reduced risk of disease progression [5, 6, 7].

Periodontal vertical bony defects (intrabony defects) have been associated with a higher risk of progression and eventually tooth loss [8]. Therefore, they are considered sites requiring therapy, often beyond NSPT. The treatment of intrabony defects has gradually evolved from radical surgical elimination of the defect by removal of some of the adjacent healthy supportive or non-supportive bone [9], to more conservative surgical approaches [10] and then to regenerative surgical procedures resulting in regeneration of periodontal
attachment measurable clinically, radiographically and histologically [11]. However, even these less invasive surgeries are associated with potential morbidity and high costs due to the use of bone graft and barrier materials and are not always predictable [12]. More recently, minimally-invasive surgical therapy (MIST), modified minimally-invasive surgical therapy (M-MIST) and single-flap approach [13] techniques were introduced, adapting regenerative procedures to the principles of minimally-invasive surgery. Results of studies using these techniques suggest that the use of biomaterials may not be so crucial for obtaining periodontal regeneration [14]. A recent consensus report of the American Academy of Periodontology considers surgical intervention still the treatment of choice for intrabony defects [15].

Pushing the boundaries of minimal invasiveness, a non-surgical minimally-invasive treatment protocol, named MINST, has recently been proposed for the treatment of intrabony defects [16]. A recent retrospective analysis has revealed a reduction in bony defect of approximately 3 mm for cases treated with minimally-invasive non-surgical therapy in non-smokers [17]. This improvement seems to be stable at least up to 5 years after treatment, despite no surgical intervention [18]. The effect of MINST may be mediated by improved blood flow and stable blood clot in the intrabony defect. However, no study to our knowledge has tested the efficacy of minimally-invasive non-surgical therapy compared with traditional NSPT followed by surgical intervention (M-MIST) in the osseous healing of intrabony defects.

The primary objective of this study is to compare the efficacy of a further refinement of the MINST approach (modified MINST) with a surgical approach (M-MIST) for the treatment of intrabony defects. Secondary objectives are: i) to compare radiographic intrabony angle change from before to after treatment and between groups; ii) to investigate the association between local factors (gingival blood flow, GCF concentration of inflammatory
markers, lipids and growth factors, bacterial presence) and intrabony defect depth healing, iii) to investigate the association between patient-based demographic and health-related factors (age, gender, medical history, body mass index) and intrabony defect depth healing.

Methods/design

This is a parallel group, single centre, examiner-blind, non-inferiority randomised controlled trial (RCT) to compare the effect of the interventions below in the healing of periodontal intrabony defects in 66 periodontitis (CP) patients:

- a novel non-surgical treatment protocol (modified MINST)
- a surgical protocol (M-MIST)

Inclusion Criteria

The following criteria will be considered for inclusion in the study:

i) Age 25-70, ii) Diagnosis of ‘Periodontitis’ stage III or IV (grades A to C), iii) Presence of ≥1 ‘intrabony defect’ (PPD, >5 mm with intrabony defect depth ≥3 mm at screening radiograph), iv) Signed informed consent.

Exclusion Criteria

i) Smoking (current or in past 5 years), ii) Medical history including diabetes or hepatic or renal disease, or other serious medical conditions or transmittable diseases, ii) History of conditions requiring prophylactic antibiotic coverage prior to invasive dental procedures, iii) Anti-inflammatory or anticoagulant therapy during the month preceding the baseline exam, iv) Systemic antibiotic therapy during the 3 months preceding the baseline exam, v) History of alcohol or drug abuse, vi) Self-reported pregnancy or lactation, vii) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that according to the investigator may increase the risk associated with trial participation, viii) Periodontal treatment to the study site within the last 12 months.
Study Design / Plan – Study Visits

All patients will be recruited from the Restorative and Periodontal new patient clinics at Barts & The London Dental Hospital, where potentially suitable new periodontitis patients will be informed about the study. Then a member of the research team will approach potentially-interested patients, will provide more information about the study procedures together with the benefits and risks of participation and will give suitable patients the Patient Information Sheet, which they will be advised to read carefully. Potential participants will be informed that they will be allowed to withdraw their participation at any stage of the study. The patients will then be contacted within 1 week to enquire about their willingness to take part in the study and to give them the opportunity to ask any questions about the study. Upon agreeing to partake, they will be offered a baseline appointment. A written informed consent (including clinical procedures and collection of study samples) will be obtained before enrolment. Informed consent will follow the Barts and The London and QMUL standard operating procedures and will be conducted by staff trained in taking consent.

Study visits

Each subject will attend between 8 and 13 study visits over a period approximately 16 months (attached Table 1 with study visit schedule and procedures). All the visits will take place in the clinics of Barts & The London Dental Hospital. The schedule of assessment is also presented in Figure 1 (‘Study plan and visits’) and in Figure 2 in the form of CONSORT diagram.

Study procedures

Medical history

A complete medical history will be obtained at the screening visit, including demographic
background information and dental status information. This will be reviewed and updated throughout the duration of the study. All concomitant medications, procedures and adjunctive product use will be monitored and recorded throughout the study. Tobacco use history will be recorded at baseline based on self-report. Body Mass Index will be calculated after measuring participants’ height and weight.

Clinical periodontal assessment
The following periodontal measurements will be taken by the calibrated examiner (author VK) at six sites/tooth using a manual University of North Carolina (UNC-15) periodontal probe (Hu-Friedy, Chicago, IL): dichotomous full mouth plaque scores (FMPS) [19], full mouth probing pocket depth (PPD), recession of the gingival margin from the cemento-enamel junction (CEJ), dichotomous 6-point bleeding on probing (FMBS) [19], tooth mobility [20] and furcation involvement with a Nabers probe (Hu-Friedy, Chicago, IL) [21]. Clinical attachment level (CAL) will be calculated as PPD+ recession. The Early Healing Index [22] will be measured for controls 1 week after surgery. Dentine/root sensitivity (DS/RS) will be assessed on the tested intrabony tooth and on the 2 neighboring teeth, following isolation using cotton wool rolls, by using an evaporative/thermal stimuli from a one second blast of air from a dental unit syringe at 40-65 psi (19°-23°C) directed perpendicular to the tooth surface at a distance of 0.5-1cm to the exposed root surface (Evaporative Examination) [23]. Following the air blast, the subject will be given a Visual Analogue Scale (VAS) form to complete each assessment. The VAS is scored from 0= no pain to 10=extreme pain and the subject can indicate the degree of discomfort by indicating either a numerical value from 0-10 or by marking vertically across the VAS scale.

Repeatability
Following initial training, for a repeatability exercise the examiner and back-up examiner
will perform repeated examinations on 10 subjects for PPD and recession with at least 15 minutes separation. Upon completion of all measurements, intra-examiner repeatability for PPD measurements will be assessed. In order to test inter-examiner repeatability, at least 10 subjects will be probed twice (once by each examiner). The reproducibility of the examiner will be tested using the Bland-Altman approach [24] and by calculating Lin’s concordance correlation coefficient [25]. A co-efficient of repeatability less than ± 2mm in 95% of the cases is considered acceptable. If this target is not achieved, further examiner assessment and training will be carried out before a new reproducibility exercise.

Clinical photographs
Clinical photographs and videos of procedures carried out, will be taken in some of the study visits for better documentation of cases and will be anonymized and stored in the study database.

Radiographic analyses
Standardised radiographs of selected study sites will be taken at baseline and at the 9-month and 15-month follow-up visits using the parallel technique with a customised holder and an occlusal platform, which will allow a cold-cure acrylic resin occlusal registration to be made (bite index), facilitating relocation of the holder and preserving the projection geometry in subsequent radiographs. Aluminium stepwedges will be used as a densitometric reference, in an attempt to minimize errors due to variation in exposure time and/or film processing which may result in false positive analysis [26]. The linear radiographic measurement analysis will be carried out by a single calibrated examiner using semi-automated radiographic software with specific landmarks, as described by Nibali et al. [27]. In brief, horizontal and vertical bone loss of the intrabony defects will be measured after identifying the following landmarks in periapical radiographs: cemento-enamel junction (CEJ) on the tooth with the intrabony defect, most coronal part of the
alveolar bone and most apical part of the alveolar bone crest, where the periodontal ligament space was judged to retain its normal width. The radiographs will be analysed by the same trained and calibrated examiner in a masked, random order with the use of a computer software measurement tool (Emago®, Oral Diagnostic Systems, Amsterdam, Netherlands).

**Test procedure (MINST)**

Based on our previous study [17], a modified MINST protocol for this study consists of the following:

- Local anaesthesia by infiltration without adrenaline in the study site (not intrasulcular)
- Thorough debridement of the root surface up to the bottom of the periodontal pocket under local anesthesia
- Attempt to minimize the trauma to the soft tissues and especially to the papilla, using a sub-papillary access for debridement (trying not to touch the most coronal part of the interdental papilla)
- Use of exclusively piezo-electric devices with specific thin and delicate tips
- Deliberately avoid to ‘smooth’ the root surface or to perform gingival curettage
- Use of 3-4x magnification loupes
- Attempt to stimulate the formation of a stable blood clot, by natural filling of the intrabony defect with blood following debridement (no use of any subgingival rinses)

This modified protocol differs slightly from the published protocol [17] in the use of a sub-papillary access, exclusively piezo-electric devices (no curettes), the specific use of anesthesia without adrenaline and not intrasulcular, and the first subgingival probing at 6 months post-treatment (rather than 3 months). These slight refinements from the earlier studies [17] aim to further reduce tissue trauma and to stimulate a stable blood clot, for optimal healing. This modified MINST protocol will be applied to the intrabony sites and all
other affected sites in test patients. The same treatment protocol is currently being tested in a separate single-arm prospective multicenter study (clinicaltrials.gov reference NCT03741374).

**Control procedure (M-MIST)**

This will be performed as described in the literature [28,14]:

Scaling and root planing using conventional ultrasonic tips and curettes under local anaesthesia

Periodontal re-evaluation and charting 3 months later

In case of residual PPD>5mm, surgical access, with the following protocol:

Ideally, the experimental sites will be accessed with the M-MIST technique (elevation of only buccal flap with simplified or modified papilla preservation incisions, no papilla elevation) and carefully debrided.

When a defect wraps around the lingual aspect of a tooth and the M-MIST is not applicable, elevation of the inter-dental soft tissues becomes necessary and a MIST becomes the preferred approach. This consists of elevation of small buccal and lingual flaps (with modified papilla preservation incision in case of interproximal space width of at least 2 mm or otherwise simplified papilla preservation [29]

When the position of the residual buccal/lingual bony wall(s) is very deep and difficult or impossible to reach with the above-described minimal incision of the defect-associated inter-dental space, the flap(s) will be further extended mesially or distally involving one extra inter-dental space to obtain a larger flap reflection [29].

Should the FMPS not reach the threshold below 25% before surgery, additional OH instructions will be given before proceeding with surgical intervention. If after 3 additional OH sessions, the FMPS is still not below 25%, the patient will be exited from the study as not considered suitable for surgery [30]. Measurements will be taken during surgery to
characterize the defect anatomy (number of walls, depth, and width). No regenerative material/devices will be applied. Flaps will be sutured with modified internal mattress sutures (and single interrupted sutures if necessary).

Need for further treatment during and following study completion

Treatment to sites other than the selected ‘intrabony site’ throughout the study will consist of subgingival debridement (as allocated by randomization in test and control patients) and supportive therapy as per protocol. The need for other surgical interventions will be reviewed following the 15-months follow-up. Should deterioration be detected during the study in any sites, where urgent need for surgery or antibiotics is needed, this will be carried out in additional visits during the study and will be documented in the case-report forms. Following the 15-month follow-up, the possible need for further treatment will be assessed based on residual PPDs > 5mm [31, 4].

Gingival crevicular fluid (GCF) sampling

An ‘intrabony site’ (IS) and a ‘comparison site’ will be chosen for sampling for each patient among buccal sites. The ‘intrabony’ site is selected according to the inclusion definitions above. In case of multiple IS per patient, the site with deepest PPD will be chosen. The ‘comparison’ site will be a site with PPD<4mm and not bleeding on probing at the screening visit. Samples of GCF will be collected from the selected IS and CS (for both test and control subjects) at baseline, at the 3-months visit and at 9 and 15 months follow-ups, prior to periodontal probing to avoid contamination by blood. In the 20 randomly selected subjects taking part in the ‘GTI sub-study’, additional GCF sampling will be conducted at day 1- and day 5- visits following initial treatment (for both test and control subjects). Saliva will be removed from the supra-gingival area using saliva ejector and cotton rolls, being careful not to touch the gingival margin area; supra-gingival
plaque, if present, will be removed using a curette to prevent saliva and/or plaque contamination. GCF will be collected for 30 seconds using methylcellulose strips carefully placed gently at the entrance of the sulcus until slight resistance is felt. GCF volume will be routinely estimated by Periotron (OraFlow Inc., New York, U.S.A.). GCF will be immediately extracted in acidic buffer to better preserve inflammatory mediators of periodontal disease from breakdown and/or oxidative processes, which occur on major extent on the paper strips during the storage [32]. GCF samples will be then immediately placed into small conic vials and stored at -80°C until time of analysis. Samples will then be processed at the Blizard Institute, Barts and the London School of Medicine & Dentistry, where immunoassay of inflammatory molecules (including for example levels of cytokines) and growth factors (including for example BMP-2; bone morphogenetic protein-2) in the GCF will be performed. COCR and the Blizzard’s local standard operating procedures, working practices and risk assessments will be followed to ensure the integrity and viability of all samples to be anonymised, labelled, stored and transferred.

**Subgingival plaque sampling**

Following GCF collection, ‘intrabony site’ and ‘comparison site’ will have samples of subgingival plaque collected (for both test and control subjects) from the palatal-lingual aspect. Plaque samples will be collected from the selected IS and CS (for both test and control subjects) at baseline, at the 3-months visit and at 9- and 15-months follow-ups. In the 20 randomly selected subjects taking part in the ‘GTI sub-study’, additional plaque sampling will be conducted at day 1- and day 5- visits following initial treatment (for both test and control subjects). Ahead of the sampling procedure, the supra-gingival plaque will be carefully removed, the site isolated with cotton rolls and gently dried. A sterile curette will then be inserted to the bottom of the pocket and removed after a single stroke and the content will be placed in a test tube containing reduced transport fluid until time of
analysis. Plaque samples will be analysed using next generation marker DNA sequencing to characterise the subgingival microbiota in order to identify and determine the levels of key periodontal bacterial pathogens and microbial community-wide changes in sites treated with both test and control protocols.

**GTI (Geometric/Thermal Imaging) sub-study**

A random sample of 20 subjects (10 in each arm) will be randomly selected to take part in the Geometric/Thermal Imaging (GTI) sub-study. The GT image capturing is based on the principle of optical triangulation, it is non-contact and non-invasive to patient and it aims to clarify differences in the wound healing pattern and association to clinical and patient-centered outcomes between the two groups. These subjects will undergo all study visits in the same way as other subjects but will attend the additional imaging analysis at some study visits, as well as at some additional visits as outlined below. The image capture, analysis and measurements will be performed in the selected participants at baseline, day-1 and day-5 after non-surgical treatment, 3-month and 9-month follow-ups and, in the surgical group, additional measurements will be performed at 1-week and 1-month after surgery.

**Patient-reported outcomes (PROMS)**

A substantial body of evidence suggests that presence of periodontitis has a considerable effect on the quality of life of affected individuals [33]. This effect will be assessed by measuring patient-reported outcome measures (PROMs). Patient-reported outcomes will be collected using validated patient questionnaires (OIDP, EQ-5D, global ratings for periodontal health and QoL) [34, 35, 36] at baseline, 3-, 9- and 15-months follow-ups. In addition, subjects allocated to the control group (MIST) will provide PROMS at the 1-week review appointment after the surgical procedure. Furthermore, the subjects allocated to the GTI subgroup will provide PROMS at the 1- and 5-days post-treatment visits.
Statistical analysis plan

Primary Objectives and Outcomes: To investigate whether MINST is not inferior to M-MIST in terms of intrabony defect depth healing in patients with periodontitis after 15 months follow-up, measured as:

Primary outcome: Radiographic intrabony defect depth change

Secondary Outcomes:

- PPDP and CAL change (in mm)
- Inflammatory markers and growth factors in gingival crevicular fluid (GCF)
- Bacterial detection associated with presence of intrabony defects
- Gingival inflammation and healing (as measured by geometric/thermal camera imaging in a subset of 10 test and 10 control patients)
- Patient-reported outcomes

The sample size calculation was based on the assumption that the proposed modified MINST protocol is an acceptable alternative to the M-MIST protocol (non-inferiority), with the advantage of reduced costs and morbidity. A non-inferiority margin of 1 mm is considered to be the largest difference that is acceptable between MINST and M-MIST (a lower threshold than the expected difference in bone gain between regenerative surgeries and open flap debridement in intrabony defects) [12] for MINST to be adopted in clinical practices because of the associated advantages of MINST. Single flap approaches such as M-MIST have previously been reported to lead to radiographic bone gains from 1.8 mm ± 1.2 [37], 2 mm [38] to 3.5 ± 1.0 mm [14] in small trials. MINST has been reported to lead to 2.4 ± 2.1 mm radiographic bone gain in a retrospective study [17]. Therefore, we assume that the two protocols lead to the same bone gain for the sample size calculation. Accounting for a 10% drop-out rate and using a pooled standard deviation of 1.27, recruiting n=66 participants will be sufficient to confer 90% power to reject the inferiority
null hypothesis. Should the true mean bone gain difference between MINST and M-MIST be 0.19 mm in favour of M-MINST the study would retain statistical power of 80%. The primary outcome analysis will compare the intrabony defect depth between treatment groups at 15 months using a general linear model (ANCOVA) with treatment as a factor and the corresponding baseline value as a covariate and adjusting for pre-specified prognostic baseline factors (age, FMPS, BMI, defect angle, tooth mobility). For the primary efficacy endpoint, non-inferiority of M-MIST to MINST could be claimed if the lower limit of the 95% confidence interval (for the difference in mean change of radiographic intrabony defect depth change) was greater than −1.0mm. The primary outcome analysis will be the per-protocol analysis and the intention-to-treat analysis considered as sensitivity analysis. For other non-inferiority endpoints the per-protocol analysis will also be considered the main analysis. Superiority endpoint will be analysed on an intention-to-treat basis.

Subject-based and site-based analyses will be conducted. PROMs analysis will be based on linear or logistic regression (for continuous/categorical variables) comparing PROMs scores or categories of scores at follow-up (3-, 9- and 15-months post-intervention) between the two groups, accounting for the respective scores at baseline. We will also look at the minimally important difference for PROMs where applicable, such as in the case of the OIDP, and whether any difference between the two groups is clinically meaningful.

Data management

All data will be entered in a dedicated secure database application with secure web connection (REDCap). A customised REDCap project will be set up for this study and will be used to cover all data capture for the study. Different levels of access will be set up for the different end users/study team delegates. Data will be proofed for entry errors before being locked and exported for analysis.

Randomisation and allocation concealment
Following the baseline visit, all participants enrolled into the study will be randomly assigned to one of the two treatment groups and whether or not to be included into the GTI sub-study; that is, individual level randomisation to MINST, M-MIST, MINST + GTI or M-MIST + GTI will be performed using a 2:2:1:1 allocation ratio. Random permuted block randomisation with block sizes 6 and 12 will be employed. The centralised online randomisation service ‘Sealed Envelope’ with web front-end will be used ensuring allocation concealment. No minimization or stratification is planned.

**Blinding**

Due to the nature of the intervention only blinding of all outcome examiners is possible. Both participants and clinicians administering treatment will be unblinded. Members of the trial steering committee and other study team members will remain blinded to treatment allocation until the randomisation code is broken (after last follow-up data is recorded and the database locked).

**Potential Risks or Burdens for Research Participants and How to Minimise Them**

No risks or burdens are expected from the basic periodontal examination and treatment. Minor pain or discomfort may follow the sub gingival debridement and can be easily controlled by using 0.2% chlorhexidine gluconate solution rinse and, if needed, paracetamol 2x 500 mg up to 4 times a day for the first two days. The surgical interventions are also standard routine procedures and will be carefully planned and performed under local anaesthesia. The following post-operative regime will be followed in the first and second weeks following the completion of the treatment in order to minimise the patient's discomfort and risk of complications: post-operative pain will be controlled with paracetamol if required, all patients will be instructed to discontinue locally tooth brushing at the surgical site to minimise trauma and to rinse with 0.2% chlorhexidine
digluconate 2 times/day for the first 2 weeks.

Adverse Events (AEs) which may be related to Periodontal Surgery, Geometric-Thermal Images and other dental or non-dental (including samples’ collection) procedures may be recorded on the AE log based on the study medical team assessments. AEs which are assessed by the study medical team as deviating; i.e. in severity, intensity and frequency; from potentially expected AEs will be recorded on the AE log. Potentially expected AEs are commonly-reported adverse events following non-surgical and surgical periodontal therapy such as gingival bleeding, bruising and swelling in the first 2-3 days post-therapy and increase in tooth sensitivity in the first 1-2 weeks post-therapy.

Any serious adverse event (SAE) occurring to a research participant will be reported to the sponsor within 24 hours of learning of the event and to the REC within 15 days if in the opinion of the Chief Investigator the event was related to the study research procedures and unexpected.

Risk considerations for this study include the following:

1) Safety of patients’ sensitive data: we will mitigate this by following the current information governance regulations. All patients’ data held will be coded and anonymised, encrypted and physically stored in a protected (locked or in a cloud) data point.

2) Safety of dental and other procedures: all dental or other procedures (including radiographs and sample collection) proposed in this study fall within the scope of mainstream periodontal treatment. Furthermore, all clinical treatment will be performed by an appropriately trained clinician. In case of unfavourable adverse event or reaction, the study medical team will assess its severity, relatedness and potential consequences to the study patients and will make an informed decision as per the patient suitability to remain or be exited from the study. Should the patient be exited from the study he/she will be offered appropriate periodontal or dental treatment and any other support as
needed.

3) Risk of not being able to complete the study due to lack of patient recruitment: careful analysis of patient flow and current experience from other studies has estimated that 66 suitable patients could be screened and enrolled in 6-7 months. If not, study recruitment period will be extended or other contingencies will be sought after including opening more sites if needed.

Reporting of any suspected expected or unexpected serious adverse events will be communicated to the study sponsor following standard research governance protocols as well as to the REC committee approving this study. The study monitoring will be performed by the Clinical Research Facility manager and/or the study coordinator in pre-determined intervals as per monitoring and management plan. Annual & safety reports to REC committee will be submitted annually whilst notifying the REC of any corrective actions or mitigations and contingencies planned or implemented as necessary.

**Data handling and record keeping**

Barts Health NHS Trust will collect information from patients in order to contact them when needed and to make sure that relevant information about the study is recorded for their care. Barts Health NHS Trust will keep identifiable information about patients in this study for 20 years after the study has finished. Information related to participants will be kept confidential and managed in accordance with the General Data Protection Regulation (GDPR) (EU) 2016/679 Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

**Monitoring and auditing**

Internal regular monitoring visits will take place to ensure that all trial’s related activities are conducted according to the trial protocol and the data were recorded, analysed and
accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Internal audits may be conducted by a sponsor’s- QMUL- or funder- Bart’s Charity for this study- representative if deemed necessary. The QMUL Centre for Oral Clinical Research (COCR) will internally monitor and manage the study on behalf of the sponsor (QMUL). The trial management and monitoring plan (including the frequency of monitoring visits), the level of Source Data Verification (SDV) and percentage of consent monitoring or the level of proportional review for data transfer from source docs to Case Report Forms (CRFs) will be set up at the beginning of the trial by COCR delegated personnel. Any arrangement for monitoring and auditing the conduct of the study will be critically examined to ensure it complies with the relevant parties’ allocation of responsibilities as set out in the Research Governance Framework.

**Trial committees**

Focus groups including study investigators, nurses, patients and members of the public were organised in the planning stages of the study and then to review study documents including patient information sheet and consent form. A study specific Trial Management Group (TMG) will take place ideally every month including the study CI as well as the relevant co-investigators and other team members. TMGs are aimed at discussing the routine management of this research project and any clinical or other type of deviations from the study protocol, sponsor’s SOPs, GCP and the applicable regulatory requirement(s). A Trial Steering Committee (TSC) including the trial statistician, the study CI, the imaging scientist, co-investigators or collaborators, the study data management and coordinating team, a member of the public and a patient representative will convene ideally every 6 months. Study focus groups including 1 or 2 study investigators, study coordinator or nurse and a panel of 4-5 individuals selected from hospital patients and
public will be held annually starting from the set-up phase, in order to advice on study design and delivery.

**Dissemination**

Results of this study are likely to be disseminated through scientific dental journals with open access policies and International periodontal conferences. Public access to the full protocol, participant-level dataset, and statistical code will be provided upon reasonable request. We also plan to disseminate our research findings in a language that needs to be easily understood by a lay person attending the local public engagement meetings, through leaflet distribution and our webpages and with the use of patient forums. Dissemination of project outcomes will also take place across the larger Bart’s Health communities and stakeholders, setting up future research pathways, support and collaborative agreements.

**Discussion**

This study will produce data on the efficacy and potential applicability of a modified MINST protocol for the treatment of periodontal intrabony defects. If shown to be non-inferior (in terms of radiographic and clinical defect reductions) to the tested surgical approach, MINST might be suggested potentially as an alternative to the use of surgical procedures, being a less invasive option. Results of the study will be published in peer-reviewed journals and published at International conferences following completion of all study analyses.

**TRIAL STATUS**

Protocol version number 1.2 dated 13 September 2018 has received ethics approval in November 2018 as stated above. Patient recruitment started at the beginning of 2019 and be completed by late 2019-early 2020, after which we will only follow up on existing study patients. Any necessary amendment to the study protocol will be submitted for
ethics approval and, upon approval, the relevant changes will be made to the clinicaltrials.gov database and the Trials publication.

Abbreviations

AE Adverse Event
BOP Bleeding On Probing
CAL Clinical Attachment Loss/Level
CI Chief Investigator
CRF Case Report Form
CS Control Site
DS/SR Dentine/Root Sensitivity
FMBS Full Mouth Bleeding Score
FMPS Full Mouth Plaque Score
GCF Gingival Crevicular Fluid
GCP Good Clinical Practice
GT Geometric-Thermal
GTI Geometric-Thermal Imaging
IS Intrabony site
MIST Minimally-Invasive Surgical Therapy
M-MIST Modified Minimally-Invasive Surgical Therapy
NHS REC National Health Service Research Ethics Committee
NSPT Non-Surgical Periodontal Therapy
OHR-QoL Oral Health-Related Quality of Life
OIDP Oral Impact on Daily Performances
PROM Patient-Reported Outcomes
PPD Probing Pocket Depth
RCT Randomised Controlled Trial
REC Research Ethics Committee
SAE Serious Adverse Event
SDV Source Document Verification
SOP Standard Operating Procedure
TMG Trial Management Group
TSC Trial Steering Committee

Declarations

Ethics approval and consent to participate:
This study received ethics approval by London-Camden & Kings Cross NHS Research Ethics Committee and Health Research Authority (HRA) in November 2018 (REC reference 18/LO/1956). The Principal Investigator will ensure that the study is carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. Each patient will be required to sign an Informed Consent (IC) prior to study enrolment.

Consent for publication: Consent for publication of the study methods and results has been sought from patients as part of the informed consent process. No individual/identifiable patient data will be published.

Availability of data and material: The final database will be accessible for all members of the research team (the authors of this protocol). The datasets generated will not be publicly available. However, following study completion, study data will be made available in de-identified form by the corresponding author for any reasonable request.

Competing interests: The authors report no competing interests in relation to this study

Funding: This study has received funding by a large Barts charity project grant (reference
MGU0389) awarded in November 2017. The funding body was not involved in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions: Authors LN and ND contributed to conception of the study. All authors indicated in the author list have contributed to study design. Author LN is the study’s Chief Investigator. Authors ND, NG, LZ, RA and GT are named co-investigators. The study protocol was prepared independent of the study funder (Barts charity). The study sponsor has ultimate authority in study design, collection, management, analysis and interpretation of data and has agreed with the decision to submit the report for publication.

Acknowledgements: We would like to acknowledge the study sponsor, Queen Mary University of London (QMUL) Joint Research Management Office and the Clinical Director, Prof. Philip Taylor for facilitating the conduct of the study. Sponsor’s contact person: Dr Mays Jawad, Research and Governance Operations Manager, Joint Research Management Office, email: sponsorsrep@bartshealth.nhs.uk.

References

[1] Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014 Nov; 93(11): 1045-53.

[2] Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Clin Periodontol. 2018; 45 Suppl 20:S149-S161.

[3] Papapanou, P. N. & Tonetti, M. S. Diagnosis and epidemiology of periodontal osseous lesions. Periodontology 2000. 2000; 22: 8–21.

[4] Heitz-Mayfield LJ, Lang NP. Surgical and nonsurgical periodontal therapy. Learned and
unlearned concepts. Periodontol 2000. 2013 Jun;62(1):218-31.

[5] Claffey N, Egelberg J. Clinical indicators of probing attachment loss following initial periodontal treatment in advanced periodontitis patients. J Clin Periodontol. 1995 Sep; 22(9): 690-696.

[6] Armitage GC. Periodontal diseases: diagnosis. Ann Periodontol. 1996 Nov;1(1):37-215.

[7] Paulander J, Wennström JL, Axelsson P, Lindhe J. Some risk factors for periodontal bone loss in 50-year-old individuals. A 10-year cohort study. J Clin Periodontol. 2004 Jul;31(7):489-96.

[8] Papapanou, P. N. & Wennstrom, J. L. The angular bony defect as indicator of further alveolar bone loss. Journal of Clinical Periodontology. 1991; 18, 317-322.

[9] Friedman, N. Periodontal osseous surgery. The apically repositioned flap. Journal of Periodontology. 1955; 33: 328-340.

[10] Rosling, B., Lindhe, J. & Nyman, S. Influence of professional tooth cleaning on bone regeneration following periodontal surgery. Journal of Dental Research. 1975; 54, 211-217.

[11] Cortellini, P. & Tonetti, M. S. Focus on infrabony defects: guided tissue regeneration. Periodontology 2000. 2000; 22: 104-132.

[12] Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. Cochrane Database Syst Rev. 2006 Apr 19; (2): CD001724

[13] Trombelli, L., Farina, R., Franceschetti, G. & Minenna, L. Single flap approach in periodontal reconstructive surgery (article in italian). Dental Cadmos 2007; 8: 15-25.

[14] Cortellini P, Tonetti MS. Clinical and radiographic outcomes of the modified minimally invasive surgical technique with and without regenerative materials: a randomized-controlled trial in intra-bony defects. J Clin Periodontol. 2011; 38(4):365-73.
[15] Reynolds MA, Kao RT, Camargo PM, Caton JG, Clem DS, Fiorellini JP, Geisinger ML, Mills MP, Nares S, Nevins ML. Periodontal regeneration - intrabony defects: a consensus report from the AAP Regeneration Workshop. J Periodontol. 2015; 86(2 Suppl):S105-7.

[16] Ribeiro, F.V., Casarin, R.C., Palma, M.A., Junior, F.H., Sallum, E.A. & Casati, M.Z. Clinical and patient-centered outcomes after minimally invasive non-surgical or surgical approaches for the treatment of intrabony defects: a randomized clinical trial. Journal of Periodontology 2001; 82: 1256-66.

[17] Nibali L, Pometti D, Chen TT, Tu YK. Minimally invasive non-surgical approach for the treatment of periodontal intrabony defects: a retrospective analysis. J Clin Periodontol. 2015; 42(9):853-9.

[18] Nibali L, Yeh YC, Pometti D, Tu YK. Long-term stability of intrabony defects treated with minimally invasive non-surgical therapy. J Clin Periodontol 2018 Oct 11. doi: 10.1111/jcpe.13021.

[19] Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, Tonetti MS. Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized placebo-controlled clinical trial. J Clin Periodontol. 2005 Oct; 32(10): 1096-107.

[20] Laster L, LAudenbach KW, Stoller NH. An evaluation of clinical tooth mobility measurements. J Periodontol. 1975 Oct; 46(10):603-607.

[21] Hamp, S. E., Nyman, S. & Lindhe, J. Periodontal treatment of multirooted teeth. Results after 5 years. Journal of Clinical Periodontology. 1975; 2, 126-135.

[22] Wachtel, H., Schenk, G., Bohm, S., Weng, D., Zuhr, O. & Hurzeler, M. B. Microsurgical access flap and enamel matrix derivative for the treatment of periodontal intrabony defects: a controlled clinical study. Journal of Clinical Periodontology. 2003; 30, 496– 504.

[23] Chabanski MB, Gillam DG, Bulman JS, Newman HN. Clinical evaluation of cervical
dentine sensitivity in a population of patients referred to a specialist periodontology department: a pilot study. J Oral Rehabil. 1997; 24(9):666-72.

[24] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 327 (8476): 307-10.

[25] Lin Lik "A concordance correlation coefficient to evaluate reproducibility". Biometrics. 1989; 45 (1): 255-268.

[26] Duckworth JE, Judy PF, Goodson JM, Socransky SS. A method for the geometric and densitometric standardization of intraoral radiographs. J Periodontol. 1983 Jul;54(7):435-40.

[27] Nibali L, Pometti D, Tu YK, Donos N. Clinical and radiographic outcomes following non-surgical therapy of periodontal infrabony defects: a retrospective study. J Clin Periodontol. 2011 Jan; 38(1): 50-7.

[28] Cortellini P, Tonetti MS. Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. J Clin Periodontol. 2009 Feb; 36(2): 157-63.

[29] Cortellini P, Tonetti MS. A minimally invasive surgical technique with an enamel matrix derivative in the regenerative treatment of intra-bony defects: a novel approach to limit morbidity. J Clin Periodontol. 2007 Jan; 34(1): 87-93.

[30] Nyman S, Lindhe J, Rosling B. Periodontal surgery in plaque-infected dentitions. J Clin Periodontol. 1977 Nov; 4(4): 240-9.

[31] Serino G, Rosling B, Ramberg P, Socransky SS, Lindhe J. Initial outcome and long-term effect of surgical and non-surgical treatment of advanced periodontal disease. J Clin Periodontol. 2001 Oct; 28(10): 910-6.

[32] Preianò M, Maggisano G, Lombardo N, Montalcini T, Paduano S, Pelaia G, Savino R, Terracciano R. Influence of storage conditions on MALDI-TOF MS profiling of gingival
crevicular fluid: Implications on the role of S100A8 and S100A9 for clinical and proteomic based diagnostic investigations. Proteomics 2016; 16: 1033-45.

[33] Buset SL, Walter C, Friedmann A, Weiger R, Borgnakke WS, Zitzmann NU. Are periodontal diseases really silent? A systematic review of their effect on quality of life. J Clin Periodontol. 2016 Apr; 43(4): 333-44.

[34] Tsakos G, Marcenes W, Sheiham A. Evaluation of a modified version of the index of Oral Impacts On Daily Performances (OIDP) in elderly populations in two European countries. Gerodontology. 2001 Dec;18(2):121-30.

[35] Locker D, Quiñonez C. To what extent do oral disorders compromise the quality of life? Community Dent Oral Epidemiol. 2011 Feb;39(1):3-11.

[36] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-36.

[37] Mishra A, Avula H, Pathakota KR, Avula J. Efficacy of modified minimally invasive surgical technique in the treatment of human intrabony defects with or without use of rhPDGF-BB gel: a randomized controlled trial. J Clin Periodontol. 2013 Feb; 40(2): 172-9.

[38] Schincaglia GP, Hebert E, Farina R, Simonelli A, Trombelli L. Single versus double flap approach in periodontal regenerative treatment. J Clin Periodontol 2015: 42: 557–566.

Tables

Table 1
| Protocol Procedures                                    | Visit 1 | Visit 2 | Visit 2a | Visit 2b | Visit 3 | Visit 4 | 3-Month Post-Treatment |
|--------------------------------------------------------|---------|---------|----------|----------|---------|--------|------------------------|
|                                                        | Baseline| Side I  | 1d post  | 5d post  | Side II | Treatment |                        |
|                                                        | Treatment|         | treatment| treatment|         |         |                        |
|                                                        | Week 0  | GTI      | GTI      |          |         |         |                        |
|                                                        |         | subgroup | subgroup |          |         |         |                        |
| Verification                                           | x       |          |          |          |         |         |                        |
| Inclusion/Exclusion                                    |         |          |          |          |         |         |                        |
| Informed consent                                       |         |          |          |          |         |         |                        |
|                                                        |         |          |          |          |         |         |                        |
| Medical/Dental History & Updates                       | x       | x       | x        | x        | x       | x       | x                      |
| Demographics                                           |         |          |          |          |         |         |                        |
| Height, Weight, Waist circumference                    | x       |          |          |          |         |         |                        |
| 3D facial imaging                                      | x       | x       | x        |          |         | x       |                        |
| Periodontal measurements (PPD, REC, BOP, mobility and  | x       |          |          |          |         |         | x                      |
| furcation involvement                                   |         |          |          |          |         |         |                        |
| Plaque assessment                                      | x       |          |          |          |         |         | x                      |
| Patient-reported outcomes (PROMs)                      | x       | x       | x        |          |         | x       | x                      |
| Early Healing Index                                    | x       |          |          |          |         |         |                        |
| Standardized X-Ray                                     |         |          |          |          |         |         | x                      |
| GCF collection                                          | x       | x       | x        |          |         |         | x                      |
| Sub-gingival plaque collection/saliva                  | x       | x       | x        |          |         |         | x                      |
| Debridement                                            | x       |          |          |          |         |         | x                      |
| Impression for radiographic stent                      | x       |          |          |          |         |         |                        |
| Dentine/root sensitivity measurements                   | x       | x       | x        | x        |         |         | x                      |

**Figures**
**Figure 1**

Flowchart of study plan and visits.
CONSORT 2010 FLOW DIAGRAM

Figure 2

CONSORT flow diagram.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to
download.
SPIRIT-Checklist-.doc