Official Title: Platelet-rich Fibrin With Minocycline Versus Arestin in Non-surgical Periodontal Therapy: A Split-Mouth Randomized Controlled Clinical Trial
Unique Protocol ID: 12625-NEstrin
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Principal Investigator: Dr. Nathan Estrin
Brief Title: PRF + Minocycline vs Arestin in Non-surgical Perio Therapy
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Abstract

Periodontitis is a multifactorial disease drive by a dysbiotic microbiome.[1] In a recent publication, the American Academy of Periodontology and the European Federation of Periodontology introduced a new multidimensional classification of periodontal and peri-implant diseases and conditions, segmenting periodontitis by stages (I-IV) based on disease severity and management complexity, and grades (A-C) based on risk of progression and treatment response.[1] Non-surgical treatment remains the foundational, first line of defense with scaling and root planing, however several adjunctive therapies have shown promise in enhancing outcomes. These include platelet-rich fibrin (PRF), [2] and local antibiotics such as minocycline.[3]

Objective

This project aims to investigate and compare PRF with minocycline compared to Arestin when utilized as adjunctive therapies in the non-surgical management of Stage II or Stage III and Grade A or B periodontitis.

Project Design

This research will be a 6-month randomized trial involving a patient population diagnosed with Stage II or III periodontitis. The treatment groups and modalities will all randomly assigned to different sites within the same individual. Thus, the subject serves as their own control and not assigned to one specific group.

Background Information and Scientific Rationale

Periodontitis is a multifactorial disease caused by a dysbiotic microbiome.[1] In a recent publication, an organizing committee of the American Academy of Periodontology and the European Federation of Periodontology reported a consensus of a new classification of periodontal and peri-implant diseases and conditions.[1] The 2017 workshop resulted in a new classification of periodontitis characterized in a multidimensional staging and grading system. The Stages, based on the severity and complexity of management were defined as Stage I: Initial periodontitis; Stage II: moderate periodontitis; Stage III: Severe periodontitis with potential for additional tooth loss; Stage IV: Severe Periodontitis with potential for loss of dentition.[1] The grades were based on the evidence of risk of rapid progression and anticipated treatment response. Grade A: slow rate of progression, Grade B: moderate rate of progression, Grade C: rapid rate of progression.[1]

There are many different treatment modalities in assessing periodontal disease. Conventionally, the first phase of treatment includes non-surgical therapy with ultrasonic scalers and hand instruments. However, evidence is accumulating to support many adjunctive treatment

modalities to non-surgical therapy. These treatment modalities include the use of growth factors such as platelet rich fibrin (PRF)[2], as well as local antibiotics[3].

Platelet rich fibrin is a fibrin matrix in which platelet cytokines, growth factors, and cells are trapped in a fibrin clot and utilized in various medical and dental specialties including periodontics, dermatology, and orthopedics.[4] Having been discovered in 1974, platelet concentrates are on the forefront of regenerative medicine, and have recently shown impressive results in regenerating the periodontal supporting structures.[2, 4] Given that the platelets are derived from the patient's own blood draw, there are very little risks involved in using this treatment. However, possible risks with PRF including common risks associated with a normal blood draw including pain, bleeding, fainting, bruising, and hematoma. To minimize these risks, all blood draws in this study will be completed be a qualified member of the research team.

Participant Selection

Participants will receive comprehensive information regarding the treatment procedure, materials utilized, and potential risks or complications to ensure full understanding. This research will encompass a comprehensive and inclusive patient selection process to ensure a diverse and representative sample. Eligible participants will be adults aged 18-65 with diagnosed Stage II or III Periodontal Disease. Efforts will be made to include individuals from various racial, ethnic, and socioeconomic backgrounds, as well as different genders. Exclusion criteria will be carefully defined to maintain the study's integrity while prioritizing inclusivity. If the subject decides to participate in the study, subjects will be given ample time to review the consent form and ask any questions before signing. Subjects will be given a copy of the informed consent for their reference. Participation in the study is entirely voluntary and they can withdraw at any time without penalty. Women with the potential for childbearing will be asked to complete a pregnancy test during the screening process. Throughout the study, it is a requirement for female participants to use an approved method of birth control. Acceptable methods include abstinence, oral contraceptives, contraceptive injections, intrauterine devices, double barrier methods, contraceptive patches, or male partner sterilization. Importantly, women with childbearing potential will not face exclusion from participation in the study.

Inclusion Criteria

- •Male and Female subjects age 18-85 with Stage II or III Periodontitis according to the 2017 periodontal classification.
- •Validation of diagnosis through periodontal charting and necessary radiographs

Exclusion Criteria

- •Previously treated periodontal disease (within the last 6 months)
- •Stage I or Stage IV Periodontitis
- •Patients with a plaque score greater than 30%
- •Radiation or immunosuppressive therapy
- •Neurologic disease or disorder
- •Major mechanical obstruction to the mouth opening
- •Acute capsulitis
- •Bone metabolic disease
- •Current systemic antibiotic treatment or within 3 months prior to the study
- •Drug addiction or alcohol abuse

•Pregnancy, planning to become pregnant and or nursing
•Type 2 uncontrolled diabetics

Enrollment
This multi-site study is expected to enroll a total of up to 20 subjects.

Site Recruitment
A periodontist practicing at Lakewood Ranch dental will be the target site of the study.

Data Analysis and Interpretation
All collected data, including personal and medical information, is handled with the highest level of security and confidentiality to uphold the privacy and rights of the participant. The informed consent process, a key component of the protocol, clearly communicates to participants how their data will be treated, emphasizing the commitment to confidentiality. Data collection, storage, and transmission procedures incorporate high-security measures, including encryption and password protection, to prevent unauthorized access. Personally identifiable information is carefully managed, with a focus on anonymization or de-identification wherever possible to minimize the risk of participant identification. The research team is granted access only on a need-to-know basis, and strict access controls are implemented. Regular monitoring, audits, and compliance checks are conducted to ensure that data confidentiality measures are consistently followed throughout the study, promoting trust among participants and maintaining the integrity of the study. Safeguarding data confidentiality is of utmost importance to uphold the privacy and rights of study participants. This study will undertake a comprehensive analysis to compare outcomes across distinct treatment groups. The primary focus will involve the improvement in periodontal parameters within these groups on the same subject. Additionally, a meticulous assessment of the safety profile associated with the treatment groups will be conducted, considering any reported adverse events. The goal is to draw conclusive findings including the efficacy and safety of the varying treatment groups in treating periodontal disease.

Compensation to Participants
Participants will not receive any type of compensation or payment for their participation in the study.

Financial Responsibility
In our commitment to making research accessible and inclusive, there will be no cost associated with participation in this study. This means that there will be no fees, charges, or expenses incurred by participants throughout the study. Our goal is to ensure that everyone interested in contributing to the advancement of knowledge can do so without financial constraints. Participation is not only crucial to the success of our research but also contributes to creating a more equitable and accessible research environment for all.
In the case of an adverse event (AE) or severe adverse event (SAE) directly associated with the study, participants will not be financially responsible for any consequences resulting from their participation in the study. Should a serious AE occur, any associated medical expenses or required interventions will be covered by the research team. We are fully committed to providing support and resources to manage and address any unexpected challenges that may arise, reaffirming our commitment to the ethical and responsible conduct of research.

Adverse Event Reporting

Adverse event reporting aims to ensure participant safety, facilitate the evaluation of the intervention's safety profile, and contribute to the overall understanding of potential risks associated with the treatment groups and non-surgical treatment of periodontal disease. When an adverse event (AE) or severe adverse event (SAE) occurs, it will be promptly and accurately documented. The AE or SAE will be classified in nature, severity and relation to laser therapy and the other adjunctive applications. It will be reported to all parties including the regulatory authority and ethics committee. The subject will be closely followed until the AE or SAE has been resolved. Timely and transparent reporting is essential for maintaining the integrity of the study, protecting participant welfare, and informing regulatory decisions to ensure the ongoing safety and efficacy of medical interventions.

Principle Investigator Safety Monitoring

1.) Adverse Event Monitoring:
    a. Evaluation of any adverse events (AEs) or serious adverse events (SAEs), which are unfavorable or unintended medical occurrences, to determine their nature, severity, and relationship to the intervention.

2.) Data Collection and Analysis:
    a. Continuous collection and analysis of safety-related data including participant health status and reported symptoms, to identify any patterns or trends that may indicate safety concerns.
    b. Data collection will take place at the second maintenance visit (6 months after the non-surgical therapy and will mark conclusion of study)

3.) Regular Assessments:
    a. Assessment will be conducted at each visit to monitor for potential side effects, complications, or changes in health status related to the intervention.
    b. Each maintenance visit will include a supragingival cleaning.

4.) Compliance with Protocols:
    a. All treatment protocols will be followed, including adherence to safety procedures and guidelines outlined in ethical standards and regulatory requirements.

5.) Communication:
    a. Clear communication with the principal investigator, research staff, and participants to promptly report and address any safety concerns or adverse events.

6.) Ethical Oversight:

a. Ethical principles and guidelines will be followed to prioritize participant safety and ensure that the research is conducted with the highest standards of integrity.

7.) Regulatory Reporting:
    a. Reporting and monitoring of any adverse events and safety-related data directly to the institutional review boards (IRB) and all related parties.

8.) Risk-Benefit Assessment:
    a. Continued assessment of the overall risk-benefit profile of the intervention to determine whether the potential benefits outweigh the risks and whether any modifications to the study protocol are necessary.

9.) Documentation:
    a. Through documentation of all safety-related information, including adverse events, their resolution, and any actions taken to address safety concerns.

Data Collection

Ensuring data confidentiality is paramount in a research protocol to protect the privacy of participants and maintain the integrity of the study. The protocol outlines rigorous measures to safeguard all collected data, including personal, medical, and potentially sensitive information related to periodontal disease. Key considerations for data confidentiality in a research protocol include:

Informed Consent Process:

Clearly articulate to participants how their data will be handled, emphasizing the importance of confidentiality during the informed consent process. Verbalize the extent to which their information will be anonymized or de-identified to protect their identity.

Resources Available

This study will be facilitated by Dr. Richard Miron and Dr. Nathan Estrin, both are trained in GCP, HSR, and HIPPA. Staff is also trained in data collection, documentation, and storage.

Early Withdrawal of Subjects

Ideally, each participant should stay engaged in the study until the mandated follow-up period concludes. Nevertheless, participation in any study is entirely voluntary, and participants retain the right to withdraw at any time without facing penalties or loss of benefits. Possible reasons for discontinuation may encompass but are not restricted to, the following:

- Unacceptable adverse experience
- The subject is lost to follow-up
- The subject becomes pregnant or wishes to become pregnant
- Subjects withdraw consent for any reason
- Investigators withdraw in the best interest of the subject(s)
- Replacement of Screen Fails and Early Termination
- Study Termination

For those subjects who discontinue participation early, each subject will be followed for 30 days for adverse event monitoring (serious adverse reactions will be monitored for 90 days) after discontinuation. Monitoring of adverse reactions may be done by telephone at the study site director's discretion.

Interventions

All subjects will undergo scaling and root planing with a cavitron, lasers, and conventional curettes at all sites and receive oral hygiene instructions (OHI). After non-surgical periodontal therapy, one interproximal site will be assigned to receive PRF + minocycline while another interproximal site will receive Arestin as adjunctive therapies. Assignment of the treatment groups to the patient's dentition will be randomly selected by a member of the research team.

A detailed breakdown of the treatment groups is listed below:

1) PRF mixed with Minocycline
2) Arestin

Participants diagnosed with Stage II or III periodontitis who wish to participate in this study. These treatment groups and modalities are all completed at different sites within the same individual. Thus, the subject serves as their own control and not assigned to one specific group.

Methods

Once patients are placed in their corresponding group, they will undergo scaling and root planing (SRP) to be completed in one visit. After completion of the second scaling and root planing, the adjunctive treatment will be performed in the same visit. The patient will return two-weeks post-operatively to review home care. They will have a supragingival periodontal maintenance appointment at 3-months after the SRP visit and again at 6-months. At the 6-month periodontal maintenance, periodontal parameters will be recorded.

Therapeutic Material Preparation

Blood will be collected through an aseptic technique. Using a butterfly needle set and vacutainer tubes before centrifuged. Minocycline will be retrieved from Apothecare Pharmacy and a dose of 2mg will be mixed in with the PRF.

Scaling and Root-Planing Protocol

Patients will undergo scaling and root planing by a study personnel utilizing a combination of hand instruments and ultrasonic device to remove all calculus. An ODU-11/12 explorer will be utilized to ensure complete removal of calculus and smooth root surfaces. Left and right sides will be completed at the same visit according to standard dental protocols.

Oral Hygiene Visit

Patients will be re-evaluated 2 weeks after the second scaling and root planing visit to review proper oral hygiene and ensure no post-operative complications.

Periodontal Maintenance Treatment

Patients will be placed on a 3-month periodontal maintenance with data collection occurring at the second maintenance (6-months). They will also have supragingival scaling completed with curettes and ultrasonic device completed by a trained study personnel. The first maintenance will begin 3 months after the scaling and root planing visit until the 6-year conclusion of the study (2 periodontal maintenance visits).

Study Timeline

Visit 1 - Screening/Baseline

- Informed Consent
- Medical History
- HIPPA Form
- Urine HCG test if applicable
- Inclusion/Exclusion Criteria
- Periodontal charting
- Fasting blood draw

Visit 2- Treatment

- Treatment (Scaling and Root Planing both sides with adjunctive treatment groups)

Visit 3- 2 week Evaluation

- Review oral hygiene instructions.

Visit 4- Three-month Periodontal maintenance

- Supragingival scaling
- Review oral hygiene instructions

Visit 5- six-month Periodontal maintenance

- Supragingival scaling
- Complete periodontal charting

Periodontal Examination - Measurements in mm - absent (0) / present (1) Date:…./…./…. Clinical parameters: Probing Depth (PD), Gingival Bleeding (GB), Recession (Rec), Clinical Attachment Loss (CAL), Missing teeth (MT)

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Publication Upon the conclusion of the study, Dr. Richard Miron BMSc, MSc, PhD, DDS will author and publish the research. The scientific article aims to enhance the treatment of patients with periodontal disease and diabetes.

Conclusion

The objective of this project is to compare PRF with Minocycline to Arestin for managing periodontal disease in individuals with periodontal disease in Stage I and Stage II periodontal patients. The results of this research have the potential to advance the therapeutic choice for those experiencing active periodontal disease, ultimately enhancing their quality of life.

References

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