**Use of Extended Platelet-Rich Fibrin Membranes in Comparison to Collagen Membranes for Socket Grafting: Part 2: A Randomized Clinical Trial**

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Brief Title: E-PRF vs Collagen Membranes in Ridge Preservation

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**Study Protocol:**

## Abstract

Dental implants are often considered the gold standard to replace missing teeth. Having success with dental implants depends on the hard tissue and soft tissue remaining after tooth extractions. The first step to successful dental implant placement begins with proper socket grafting which includes placing a bone graft and membrane among other biomaterials such as platelet-rich fibrin (PRF) to prevent the collapse of the ridge that occurs after a dental extraction.

While platelet-rich fibrin is commonly utilized for ridge preservation, it is often used in conjunction with a collagen membrane due to the fact that it has a short resorption time lasting roughly 2 weeks. However, recently, it was discovered that by heating the plasma layer and denaturing the albumin, the resorption properties of PRF could be extended from 2 weeks to 4-6 months. This extended platelet-rich fibrin (e-PRF) membrane is a promising replacement to collagen membranes in various surgeries. The investigators previously demonstrated that it is a safe a feasible alternative to conventional membranes with 4 different iterations of applying the novel e-PRF membrane. However, there still lacks a comparative study to traditional collagen membranes and between the 4 different iterations.

## Objective

The purpose of this study is to evaluate and compare the effectiveness of 4 different iterations of utilizing e-PRF membranes with a collagen resorbable membrane. Each placement will receive either one of the 4 different variations of e-PRF membranes or a collagen resorbable membrane in alveolar ridge augmentation.

## Project Design

This research will be a 6-month randomized and controlled trial involving patients requiring at least one extraction and replacement with a dental implant. Participants will be recruited and randomly allocated to receive either one of the four iterations of using e-PRF membranes or a standard resorbable collagen membrane. All patients will be treated surgically with ridge preservation and dental implant placement using standard bone graft material and one of the membranes determined by their assigned group.

## Background Information and Scientific Rationale

Dental implants are often considered the gold standard to replace missing teeth. Having success with dental implants depends on the hard tissue and soft tissue remaining after tooth extractions. [1] The first step to successful dental implant placement begins with proper socket grafting which includes placing a bone graft and membrane among other biomaterials such as platelet-rich fibrin (PRF) to prevent the collapse of the ridge that occurs after a dental extraction.

While platelet-rich fibrin is commonly utilized for ridge preservation, it is often used in conjunction with a collagen membrane due to the fact that it has a short resorption time lasting roughly 2 weeks. [2-4] However, recently, it was discovered that by heating the plasma layer and denaturing the albumin, the resorption properties of PRF could be extended from 2 weeks to 4-6 months. This extended platelet-rich fibrin (e-PRF) membrane is a promising replacement to collagen

membranes in various surgeries. The investigators previously demonstrated that it is a safe a feasible alternative to conventional membranes with 4 different iterations of applying the novel e-PRF membrane.[5, 6] However, there still lacks a comparative study to traditional collagen membranes and between the 4 different iterations.

Four different techniques utilizing e-PRF membranes for ridge augmentation will be performed with a collagen membrane as a control group. These techniques include 1) e-PRF as a sole barrier membrane, 2) layering a solid-PRF membrane over the e-PRF membrane, 3) fabricating e-PRF intra-orally in gel form as a Bio-Filler, and 4) Fabricating the e-PRF membrane intra-orally under a solid-PRF membrane.

**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 18-75 requiring at least one extraction and replacement with a dental implant. 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.

Inclusion Criteria

- •Male and Female subjects aged 18-75 requiring at least one extraction and replacement with a dental implant.
- •No contraindications to dental implant placement

Exclusion Criteria

- •Smokers
- •Autoimmune disease or disorder
- •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 1 diabetes

Uncontrolled Type 2 diabetes (Anyone with an A1c >= 7%)

**Enrollment**

This single site study is expected to enroll a total of 80-100 subjects.

**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 investigators are 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 5 distinct treatment groups. The primary focus will be to evaluate differences in ridge dimensions through dental radiology and also to evaluate soft tissue healing and closure at 2 weeks post-operatiely. The goal is to draw conclusive findings regarding the healing of extraction sites, soft tissue thickness, and ridge dimensions.

**Compensation to Participants**

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

**Adverse Event Reporting**

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. The investigators are fully committed to providing support and resources to manage and address any unexpected challenges that may arise, reaffirming the investigators commitment to the ethical and responsible conduct of research.

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 blood draws and extraction and implant therapy. 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 the procedure. 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 each procedure visit

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 assessment visit will include a CBCT to assess bone levels and intra-oral photographs to evaluate healing.

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
- 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**
The study will involve the standard ridge preservation procedures in patients requiring at least one extraction and replacement with a dental implant. Data collection will be conducted at each visit. The gathered data will undergo analysis using appropriate statistical methods, with the primary objective of soft tissue thickness, quality of healing, dental implants success rate, and alveolar bone levels after surgical extraction and implant placement following a standardized protocol.

Participants requiring at least one extraction and replacement with a dental implant who wish to participate in this study will have a one of the 5 membrane variations performed during their routine extraction and bone graft. Thus, there will be five treatment groups.

Group 1 (Control): Resorbably Collagen membrane

Group 2: e-PRF as a sole barrier membrane,

Group 3: Layering a solid-PRF membrane over the e-PRF membrane,

Group 4: Fabricating e-PRF intra-orally in gel form as a Bio-Filler, and

Group 5: Fabricating the e-PRF membrane intra-orally under a solid-PRF membrane

**Methods**

Once patients are placed in their corresponding group, they will undergo ridge preservation surgery using standard bone allograft particulate mixed with PRF and secured with a membrane of their respective group. Radiographic data will be collected at conclusion of the surgery. Soft tissue thickness will be measured at the buccal and lingual aspect of the tooth. At the two-week post-operative evaluation, intra-oral photographs will be taken and sent to 3 blinded clinicians to rate the quality of healing for each case. After 3 months with new radiographic data, patient will be scheduled for implant placement with a second stage implant procedure scheduled 3 months after placement. Patients will be encouraged (but not required) to stay for 1 year after implant uncovery with peri-implant parameters recorded every 6 months.

**Therapeutic Material Preparation**

Blood will be collected through an aseptic technique. Using a butterfly needle set and vacutainer tubes.

**Extraction Protocol**

Atraumatic extractions will be completed to preserve socket walls. Complete degranulation will be completed utilizing curettes and a carbide bur on a slow-speed handpiece. After degranulation sockets will be irrigated and packed with sticky bone utilizing c/c allograft and both solid and liquid PRF. The Bio-Heat device will be utilized to heat the patient's plasma and create the various iterations of the e-PRF membrane in the 4 treatment groups, the control group will receive a resorbable collagen membrane. All membranes will be secured with chromic gut in 3-0 mattress fashion.

**Implant Placement Protocol**

After CBCT evaluation and implant planning, osteotomies for BioHorizons dental implants will be prepared according to manufacturer's instructions. All implants will be placed utilizing a delayed approach placing the implants 0-.5mm subcrestally with primary closure achieved utilizing 3.0 chromic gut. Prior to implant placement, soft tissue measurements will be taken.

**Implant Uncovery Protocol**

A 15 Blade will be utilized and full thickness flaps reflected to allow access to the implant platform. Any bone growth over top of the implant will be removed with a highspeed diamond round bur. The cover screw will be removed and stock BioHorizons healing abutment placed. 3.0 Chromic sutures will be utilized in single interrupted fashion.

**Post-op evaluations and Implant planning**

Patients will be seen 2 weeks after each procedure to ensure proper healing and any adverse reactions will be recorded. Intra-oral photographs will also be taken at each visit to evaluate wound

healing. 3-months after ridge preservation, patient will be seen for a radiographic evaluation (CBCT) for proper implant planning.

**Re-evaluation treatment (not required)**
Patients will be encouraged to return every 6 months after the surgery for data collection including probing depths.

**Periodontal Maintenance Treatment**
Patients will be placed on a 6-month maintenance with data collection (periodontal charting and fasting blood draw) occurring at each maintenance for up to 1-year after implant placement. Patients will also have supragingival scaling completed with curettes and ultrasonic device completed by a trained study personnel. The first maintenance will begin 6 months after the implant uncovery surgery visit until the 1-year follow-up conclusion of the study. The total study from extraction to final follow-up may last up to 2-years.

**Study Timeline**
Visit 1 - Screening/Baseline
- Informed Consent
- Medical History
- HIPPA Form
- Urine HCG test if applicable
- Inclusion/Exclusion Criteria
- Periodontal charting
- Necessary Radiographs (CBCT)
- Soft tissue measurements
- Intra-oral photographs

Visit 2- Treatment
- Treatment (Extraction Procedure)
- Intra-oral photographs
- Soft tissue measurement
- Necessary radiographs (CBCT)

Visit 3- Post-operative visit
- 2-week post-operative evaluation after surgical procedure.
- Intraoral photographs

Visit 4- Implant planning appointment
- Necessary Radiographs (CBCT)

Visit 5- Treatment
- Treatment (Implant placement)
- Soft tissue measurements
- Intraoral photograhs
- Peri-apical radiographs

Visit 6- Post-operative visit
- 2-week post-operative evaluation after surgical procedure.
- Intraoral photographs

Visit 7- Treatment
- Treatment (implant uncovery appointment)
- Necessary radiographs (CBCT)
- Intraoral photographs

Visit 8- Post-operative visit
- 2-week post-operative evaluation after surgical procedure.

Visit 9 (encouraged)- periodontal maintenance (6 months after implant uncovery)
- Supragingival scaling
- Complete periodontal charting
- Necessary radiographs (CBCT)

Visit 10 (encouraged)- periodontal maintenance (12 months after implant uncovery)
- Supragingival scaling
- Complete periodontal charting
- Necessary radiographs (CBCT)

**Publication** Upon the conclusion of the study, Dr. Richard Miron BMSc, MSc, PhD, DDS and Dr. Nathan Estrin DMD, MS will author and publish the research. The scientific article aims to enhance the treatment of patients undergoing extraction and dental implant treatment.

**Conclusion**

The objective of this project is to assess the effectiveness of ePRF membranes for managing extractions and dental implants by comparing different iterations of the membrane and comparing with a standard collagen membrane. The results of this research have the potential to advance the therapeutic choice for those experiencing tooth loss and replacement with dental implants, ultimately enhancing their quality of life.

References


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