March 23, 2020

ORTHODONTOCELL II CLINICAL PROTOCOL
TOOTH FIXATION AFTER BRACES OR ALIGNERS

Background:
Dental malalignment is a very common problem, with several treatment options that offer variable success in achieving desired alignment. This includes primarily the use of braces and retainers that often require 18 months of wear, but offer little to no ability to retain the teeth in the new alignment. However, data suggests that as many as 40% of individuals experience significant movement of teeth back toward original malalignment in as few as 6 months unless they continue to wear a retainer for an extended time, which is often years.

Research has led to identification of the molecular basis of tooth movement (RANKL) and tooth fixation (OPG). This knowledge has become the basis for the development of a new treatment option that is based on the use of programable bioelectric stimulation (BES) to significantly increase the local tissue expression of OPG , to minimize any movement of teeth after completion of an average of 18 months of braces or aligners, that may eliminate the need for continued use of aligners long term.

GOAL:
The goal of this study is to demonstrate the superior ability of precise BES of OPG, and two other target proteins delivered to the gums of patients that have completed a standard course orthodontic treatment with braces or aligners for tooth malalignment, to prevent tooth movement back toward original malalignment.

STUDY DESIGN:
This will be a superiority, prospective, randomized, double blind, sham-controlled, 3 arm study comparing measured tooth movement after three months of standard management following completion of a standard orthodontic treatment using braces or aligner trays. The study will compare use of a mouthpiece to deliver BES vs external passage of a an electrical wand to deliver the BES, vs use of a mouthpiece without

BES. All subjects will receive a personal BES appliance mouthpiece, but only the group randomized to aligners plus BES will receive actual stimulation, while the other subjects will have sham simulation of activating the stimulator. The BES will be delivered via an appliance with embedded electrodes that fits over braces or aligners and connected to an external stimulator.
The signals to be delivered will include only Osteoprotegrin (OPG), and SDF-1, and VEGF.

The study, including the protocol and consent form will have been approved without stipulations by a local or certified Institutional Review Board as meeting safe and good clinical practice before any subject will be enrolled. Any patient younger than 18 yrs of age must have the Consent Form signed by at least one of their parents.

Inclusion Criteria:

1. Age 14-30 yrs of age
2. Have just completed a standard course of orthodontic management using braces or aligners for tooth malalignment.
3. Able and willing to give informed consent and follow study instructions., or by signed consent of their parents if < 18 yo
4. Able to tolerate up to 20 minutes of BES
5. Able and willing to make the required study visits.

Exclusion Criteria:

1. Individuals with diminished decision-making capacity
2. Pregnancy or lactating period for females

Target Number of Participants: 30
Target Number of Enrolling Sites: 2
Length of Study: 3 months
Location of Treatments: In the office of the Principal Investigators leading this study.

Eligibility:
Any individual who has just completed a full course of orthodontic treatment for malalignment of their teeth, who meet all Inclusion and

Exclusion criteria, will be eligible for participation in the study. Each potential subject will have a brief history and examination performed by the Investigator, and if acceptable, will be provided with an overview of the Study and then provided with the Consent Form. If they choose to participate, and sign the Consent form, they will be enrolled in the Registry.

Types of Bioelectric Stimulators:

There will be two types of bioelectric stimulators used in this study, including a desk top type Mettler Stimulator which will be connected to the sports-type mouthpiece and control current initiation and termination.
A second type of stimulator will be a hand held wand that will provide bioelectric stimulation in the exact current as delivered by the Mettler but without use of a mouthpiece.

Aloe Gel: A commercially available Aloe Gel will be applied to each the gums of only those subjects randomized to bioelectric stimulation. The gel will be applied just before the mouthpiece is inserted and stimulation initiated. The purpose of the gel is to enhance conductance of the BES.

Baseline Evaluation:
Patients randomized to receive BES, either by mouthpiece or wand will have a test demonstration for a period of 20 minutes to assess any discomfort that would preclude study participation. If no problems occur during this test period of stimulatjon, patients will begin the study.

Each treatment session will be for a 20 minute period, using either the mouthpiece, wand, or sham treatment. The sport-type mouthpiece, which has been fitted with electrodes and is connected to a Mettler Bioelectric Stimulator to deliver the precise current identified to increase local tissue expression of OPG to help fix the teeth and minimize return to pre-orthodontic treatment.

Patients randomize to no active treatment with BES will be followed per standard care, but will have dental x-rays obtained at 6 and 12 weeks after enrollment in the study.

Treatment Schedule:

Frequency of Treatments: 2x's/week for one month, then 1x/week for the next 2 months
Duration of Each Treatment: 20 minutes
Location of Treatments: All treatments will take place in the office of the managing Orthodontist.

Follow Up Evaluations:
Baseline films will be taken to document the position of the teeth before treatment, and again at the end of 6 and 12 weeks, to measure and document the response to treatment.

Primary End Point: The reduction in tooth movement back toward the original position before the orthodontic treatment with braces in patients receiving BES compared to control at the end of 12 weeks of treatment
Secondary End Points:

1. Any adverse events not described above
2. Incidence of need to terminate the study for pain or other cause
3. Failure of the Bioelectric Stimulator

Data Analysis:

Data will be collected for each patient and an intermim analysis performed and analyzed after the first 15 subjects have reached the 6 week treatment period and again when all 30 subjects have met the 12 week primary end point.
Additional subjects may be enrolled into the study if approved by the IRB and Sponsor.

Control Group Treatment Post Study:

If the BES treatment proves to be superior to no therapy in the Control group at the end of the 3 month treatment period, they will be offered

Treatment with the same BES used in the treated groups, for a similar period of 12 weeks and agree to have films taken to document possible changes.