Orthodontic Tooth Movement with Accelerated Invisalign Therapy in Conjunction with Acceledent Aura®: A Randomized Clinical Trial

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SCHOOL OF DENTISTRY
GRADUATE STUDENT MASTERS THESIS DEVELOPMENT PROGRAM

ABSTRACT OF RESEARCH PLAN

STUDENT: Brian Bragassa **PROGRAM:** Orthodontics

TITLE OF PROJECT: Orthodontic tooth movement with Accelerated Invisalign therapy in conjunction with Acceledent Aura®: A Randomized Clinical Trial

THESIS ADVISOR: Dr. Ching-Chang Ko **ADVISOR'S SIGNATURE:**

COMMITTEE MEMBERS: **DATE OF SUBMISSION:** TBD
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Dr. Bill Gierie, DDS
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ABSTRACT OF RESEARCH PLAN:
Objective: The objective of this study is to investigate the effects of accelerated Invisalign and vibration therapy on rate of orthodontic tooth movement, activation of inflammation biomarkers as well as pain levels experienced during the initial 12 weeks of alignment.
Significance: Invisalign® and other advances in orthodontic technology such as clear aligners, ceramic and lingual braces have met the esthetic demands of most orthodontic patients but duration of treatment continues to be one of the most challenging aspects of orthodontic practice.[2] Accelerated orthodontic treatment presents several potential benefits and challenges to both, the orthodontic patient and provider. AcceleDent Aura® is an FDA approved class II medical device developed to accelerate tooth movement and reduce orthodontic treatment time.[7] Orthodontic providers are prescribing accelerated Invisalign in conjunction with AcceleDent vibration therapy and achieving positive results. However, it remains unclear if vibration therapy or the accelerated Invisalign aligner schedule is responsible for the increased rate of tooth movement. More clinical research is needed to provide more clarity regarding the efficacy of vibration therapy on accelerated orthodontic tooth movement.
Methods: Approximately 42 patients, between the ages of 18-65 years, will be consecutively recruited to participate in a randomized prospective clinical trial. Enrolled subjects will be randomly allocated into one of 3 groups: Standard Invisalign therapy (G1-control), Accelerated Invisalign therapy + vibration (G2) and Accelerated Invisalign therapy without vibration (G3). Data collection will include intra oral scans of both the maxillary and mandibular dentition at 5 different time points: TO (baseline), T1 (4 days), T2 (14 days), T3 (6 weeks) and T4 (12 weeks). In addition, PerioPaper strips will be used to sample gingival crevicular fluid at each of the time points listed above. Research subjects will also be asked to complete a daily diary regarding their pain level during treatment. Data analysis will be completed using digital models and Ortho Insight 3D software. Little's Irregularity Index will be used to specifically evaluate alignment of adjacent teeth and translational, and/or rotational, tooth movement will be evaluated by superimposing digital models recorded at the specific time points. Inflammation biomarkers will be analyzed with ELISA. Finally, the

statistical significance of our data will be evaluated with a 3 way repeated ANOVA as well as a post hoc comparison with Bonferri correction. P values less than .05 will be considered statistically significant.

Specific Aims:
In this study, we propose a randomized prospective clinical design to investigate effects of vibration therapy, using an AcceleDent Aura® device, on the rate of orthodontic tooth movement, activation of gingival crevicular fluid inflammation biomarkers and patient discomfort in conjunction with accelerated Invisalign therapy.

Hypothesis:
We propose vibration therapy will accelerate orthodontic tooth movement, increase inflammation biomarkers and reduce pain for orthodontic patients.

Background:
Align Technology©, Inc. developed Invisalign® in 1997 to meet the esthetic demands of orthodontic patients and providers. Invisalign patients receive a series of computer-assisted designed stereolithic clear retainers to incrementally resolve their malocclusion. Invisalign® and other advances in orthodontic technology such as clear aligners, ceramic brackets and lingual braces offer options to address the esthetic demands of most orthodontic patients but duration of treatment continues to be one of the most challenging aspects of practice.[2]

In 2008, OrthoAccel Technologies©, Inc. developed the AcceleDent device to accelerate tooth movement and reduce orthodontic treatment time. Patients receiving vibration therapy are instructed to bite down on the AcceleDent mouthpiece, which vibrates at a .25N (25 grams) force level with a 30 Hz frequency for 20 minutes per day.[15] The theory underlying AcceleDent and the use of vibration to expedite orthodontic tooth movement started in 1892 with the studies of Julius Wollf, who discovered bone adapts to pressure loads.[5] In 2001, Astronauts in space attempted to use the principles of Wolff's Law to maintain normal bone quality by working out and performing daily tasks while standing on a vibrating plate with the aid of elastic straps.[6] In 2004, the effect of vibration therapy on bone density was further supported when increased bone density and strength was noted in post-menopausal women who received whole body vibration therapy.[8] OrthoAccel claims vibration therapy using the AcceleDent device can reduce treatment time up to 50 percent by accelerating the process of bone remodeling required for orthodontic tooth movement.[9] In 2013, despite relatively little scientific evidence, the FDA approved AcceleDent as a class II medical device and orthodontic accessory to facilitate accelerated tooth movement.

Invisalign therapy in conjunction with AcceleDent has been aggressively marketed towards the esthetically sensitive patient who, not so coincidentally, is the most concerned with duration of treatment. Some orthodontic providers using vibration therapy have deviated from the standard 2-week aligner schedule and recommend a 4-day aligner schedule. Orthodontic patients receiving accelerated Invisalign therapy in conjunction with AcceleDent claim reduced treatment time by as much as 50 percent. What is responsible

for the positive results? The accelerated tooth movement might simply be the result of the accelerated Invisalign therapy, which would raise the question of whether vibration therapy and the cost associated with AcceleDent is justified.

Accelerated orthodontic tooth movement may offer many benefits to both, the patient and the orthodontist. Reduced treatment time reduces the burden of orthodontic treatment by decreasing risk for undesired treatment sequelae (e.g., white spot lesion, caries, gingivitis, etc) and potentially reduces the discomfort commonly associated with orthodontic treatment.[12] Orthodontists benefit from accelerated tooth movement for multiple reasons pertaining to practice management and increased profitability. Orthodontists using accelerated treatment techniques have reported increased profit margins due to reduced chair time and increased organic growth due to differentiation of the practice. [2]

There are also potential negative outcomes associated with accelerated orthodontic tooth movement. For the patient, there is a potential increased risk for root resorption and increased treatment fees. [2] Most orthodontists are charging between $700-800 for AcceleDent therapy in addition to the normal orthodontic fee. How can Orthodontists expect patients to pay a higher fee over a shorter treatment period? How will this affect the patient's ability to pay?

Further, the mechanism underlying any increased orthodontic tooth movement due to vibration remains unclear. Studies on a cellular level have shown a promising but complicated mechanism of how vibration may enhance activation of various cell proliferation and differentiation molecules within the periodontal ligament (PDL) stem cells as well as increase levels of gingival inflammation biomarkers.[12] For example, vibration therapy might accelerate breakdown of the cellular cytoskeleton, increase actinG trafficking into the nucleus, increase Runx2 gene expression, and thus facilitate bone formation.[1] Whether this mechanotransduction mechanism can be translated into clinical tooth movement is unknown and its clinical evidence remains to be elucidated.

In this study, we propose a randomized prospective clinical design to investigate effects of AcceleDent vibration therapy on the efficiency of tooth movement, on the activation of gingival crevicular fluid biomarkers and on patient discomfort in conjunction with accelerated Invisalign therapy.

Methods:

1. Study Design:
    a. In this study, we propose a single-blinded (Invisalign faculty) randomized prospective paralleled clinical trial to investigate effects of AcceleDent vibration therapy on the efficiency of tooth movement, on the activation of gingival crevicular fluid biomarkers and on patient discomfort in conjunction with accelerated Invisalign therapy. Enrolled subjects will be randomly allocated into one of 3 groups: Standard Invisalign therapy (G1-control), Accelerated Invisalign therapy + vibration (G2) and Accelerated Invisalign therapy without vibration (G3). Patients allocated to the standard Invisalign group will change aligners every 2

weeks while the both intervention groups will change aligners every 4 days. Patients allocated to the vibration group will receive an AcceleDent Aura device and bite down on the mouthpiece for 20 minutes/day. The AcceleDent Aura device vibrates at a .25N (25 grams) force level with a 30 Hz frequency. Data collection will include intra oral scans of both the maxillary and mandibular dentition at 5 different time points: TO (baseline), T1 (4 days), T2 (14 days), T3 (6 weeks) and T4 (12 weeks). In addition, PerioPaper strips will be used to sample gingival crevicular fluid at each of the time points listed above. Research subjects will also be asked to complete a daily diary regarding their pain level during treatment. Treatment plans for enrolled patients will be created using Invisalign's proprietary software: Clincheck Pro®. To reduce treatment plan variability and reduce potential sources of error, Dr. Bill Gierie, who is an "Elite Top 1% Invisalign provider" and also a member of the exclusive North American Invisalign Clinical Advisory Board, will approve each treatment plan. Dr. Gierie will also be blinded to any patients participation within the study in order to eliminate potential bias.

2. Recruitment:
    a. Participants will be conveniently recruited from the sample population of individuals seeking Invisalign orthodontic therapy within the UNC Graduate Orthodontic Clinic. Benefits for participants will include complementary vibration therapy using the AcceleDent Aura device, which is an estimated value of $800. Financial reimbursement will also be offered to offset any parking fees associated with the study.
3. Power Analysis:
    a. Our study will have 3 groups for evaluation: G1 control (Invisalign on a 2week aligner schedule) and 2 intervention groups, G2 and G3 (each on an accelerated 4 days aligner schedule). The only difference between the intervention groups will be the use of vibration (G2 with vibration vs G3 without vibration). The expected rate of tooth movement for G1 will be .04mm/day (.25mm/week or .5mm/2 weeks) while the expected rate of tooth movement for G2 and G3 will be .28mm/day (.5mm in 4 days). The standard deviation is assumed 0.1 for three groups. Based on our sample calculation to achieve an adequate power, we will attempt to recruit a total of 42 patients to account for a dropout rate of 30%. Ideally, we would like to have a total sample size of 21 patients to ensure each of 3 study groups will have 7 patients, which will achieve more than 0.8 power even under a Bonferroni correction for multiple comparisons.
4. Randomization:
    a. Our patients will be randomly allocated into the 3 groups based on a block randomization with size 6. The list will be independently generated by our study biostatistician.
5. Type I error and statistical significance:
    a. P values less than .05 will be considered statistically significant in the overall test
6. Inclusion Criteria:
    a. Males or females over the age of 18 years old desiring orthodontic treatment.

b. Adult dentition with all upper and lower front teeth present and any premolar and molar combination in the upper posterior of two teeth on each side.
c. Normal pulp vitality and healthy periodontal tissues as determined by intraoral exam.
d. Good health as determined by medical history.
e. Willingness and ability to comply with study procedures, attend study visits, and complete the study.
f. The ability to understand and sign a written informed consent form, which must be signed prior to initiation of study procedures.

7. Exclusion Criteria:
    a. Patient under the age of 18 years old
    b. Patients diagnosed with systemic diseases such as diabetes, hypertension (high blood pressure), temporomandibular disorders (jaw disorders), or craniofacial syndromes.
    c. Severe malocclusions that would require adjunctive procedures other than Invisalign. These include impacted teeth, closure of extractions spaces.
    d. Significant periodontal disease (> 4mm pocket depth or >2 mm of recession on upper anterior teeth).
    e. Active caries not under care of either a dentist or periodontist.
    f. Chronic daily use of any non-steroidal anti-inflammatory medication, estrogen, calcitonin, or corticosteroids.
    g. History of use or current use of any bisphosphonate medication or other medication for treatment of osteoporosis.
    h. Current smoker (must not have smoked in the last 6 months).
    i. Failing to comply with research protocols
8. Arms:
    a. Control Group (G1): 14 patients, standard Invisalign therapy with 2 week aligner schedule
    a. Intervention Group (G2): 14 patients, accelerated Invisalign + vibration
        i. AcceleDent device 20 minutes/day per manufacturer's instructions
    b. Intervention Group (G3): 14 patients, accelerated Invisalign + no vibration
7. Clinical Trial Protocol:
    a. Visit #1: Clinical Screening with UNC Orthodontic Faculty (clinical purposes only)
        i. Brief discussion of findings with patient and eligibility for Invisalign

    b. Visit #2: Clinical exam and records (clinical purposes only), 30 days post visit #1
        i. Completion of medical history
        ii. Completion of extra and intra oral exams
        iii. Completion of alginate impressions
        iv. Photographs (extra and intra oral)
        v. Xrays- Panoramic and Cephalometric

    c. Visit #3: Treatment Plan Presentation (Experimental Baseline), 60 days post visit #1

i. Clinical Procedures:
    1. Treatment plan presentation
        a. Each treatment plan will be approved by Dr. Bill Gierie who will be blinded to a patient's study participation
    2. Invisalign impressions with PVS material
ii. Research Procedures:
    1. Study recruitment
    2. Informed Consent
    3. iTero intraoral scan
    4. Completion of the Inclusion/Exclusion Case Report Form

d. Visit #4: (120 days post visit #1/Day #1 of active treatment)
    i. Clinical Procedures:
        1. Intraoral exam and intraoral photographs
        2. Deliver aligner number 1 and usage instructions
    ii. Research Procedures:
        1. Deliver AcceleDent Aura device along with instructions
        2. Collection of gingival crevicular fluid biomarkers
        3. Completion of Faces Pain Scale
        4. Deliver daily diaries

e. Visit #5: (125 days post visit #1/ Day #5 of active treatment)
    i. Clinical procedures:
        1. Deliver aligners 2-4 to accelerate Invisalign groups and aligner schedule instructions
    ii. Research Procedures:
        1. iTero intraoral scan
        2. Collection of gingival crevicular fluid biomarkers
        3. Completion of Faces Pain Scale and Adverse Event Form

f. Visit #6: (134 days post visit #1/Day #14 of active treatment)
    i. Clinical procedures
        1. Intraoral exam and intraoral photographs
        2. Place attachments (35% phosphoric acid etch, L-pop self-etching primer, composite resin, LED light curing for 30 secs)
        3. Deliver more aligners: 2-3 to control group and 5-11 to intervention groups (accelerated Invisalign)
    ii. Research Procedures:
        1. iTero intraoral scan
        2. Collection of gingival crevicular fluid biomarkers
        3. Completion of Faces Pain Scale and Adverse Event Form

g. Visit #7: (176 days post visit #1/6 weeks of after treatment)
    i. Clinical procedures:
        1. Intraoral exam and intraoral photographs

ii. Deliver more aligners: 4-6 to control group and 11-21 to intervention groups (Accelerated Invisalign)

h. Research:
    1. iTero intraoral scan
    2. Collection of gingival crevicular fluid biomarkers
    3. Completion of Faces Pain Scale and Adverse Event Form

i. Visit #8: (218 days post visit #1/12 weeks of active treatment) (End of clinical study)
    i. Clinical Procedures:
        1. Intraoral exam and photographs
        2. Deliver more aligners to both control (7-12) and intervention groups (21-30)
        3. Deliver AcceleDent Aura devices to participants in control and non-vibration intervention group.
    ii. Research Procedures:
        1. iTero intraoral scan
        2. Collection of gingival crevicular fluid biomarkers
        3. Completion of Faces Pain Scale and Adverse Event Form

j. Visit #9: (260 days post visit #1)
    i. Clinical Procedures:
        1. Intraoral exam and photographs
        2. Deliver any remaining aligners
        3. iTero Scan for any necessary revisions

k. Visit #10: (302 days post visit #1)
    i. Clinical Procedures:
        1. Intraoral exam and photographs
        2. Deliver revision aligners as needed

l. Visit #11: Treatment complete, ensure patient satisfaction
    i. Clinical Procedures:
        1. Intraoral exam and photographs
        2. Completion of alginate impression
        3. Completion of post tx pano and cephalometric xrays
        4. Deliver Essix retainers to prevent relapse

8. Data Collection:
    b. 3D intraoral scanning protocol
        i. T0- baseline
        ii. T1- 4 days
        iii. T2- 14 days
        iv. T3- 6 weeks
        v. Tfinal- 12 weeks
    c. Gingival Crevicular Fluid Sampling
        i. T0- baseline
        ii. T1- 4 days

iii. T2- 14 days
iv. T3- 6 weeks
v. Tfinal- 12 weeks

d. Orthodontic Pain Assessment
    i. Daily dairy using Faces Pain Scale

9. Monitoring Compliance:
    a. Daily diary usage log
    b. AcceleDent Fast Trac usage report

9. Adverse Events:
    a. Patients who experience an adverse event or reaction such as: uncontrolled pain or allergy will be disenrolled from the study and allowed to continue Invisalign therapy using the standard two-week aligner schedule. In addition, non-compliant patients will be disenrolled from the study and recommend to continue Invisalign therapy using the standard protocol.

10. Data Analysis:
    a. Tooth leveling and alignment
        i. Little's Index
    b. Tooth rotations and translations
        i. Euler's Law of Motion (6 degrees of freedom)
        ii. 3D surface mapping
    c. Alternative measurement options
        i. Screw Method
    d. Inflammation biomarkers within gingival crevicular fluid
        i. ELISA
    e. Orthodontic Pain Assessment
        i. Faces Pain Scale

11. Statistical Analysis:
    a. In order to complete statistical analysis for maxillary and mandibular dentition, we will compare the five time points within each group as well as the three groups across each time point.
    b. Our primary statistical method will be a three-way repeated measurement ANOVA, with the main effects being: vibration, aligner schedule, and time. The ANOVA measurement will identify significant differences within the data and the post hoc comparison will determine which specific variables are involved. In order for a relationship to be considered statistically significant, the p-value must be less than .05.
    c. One additional method for statistical analysis could be a survival analysis which would be more favorable in the case our study experiences a high volume of drop-outs during treatment.

12. Patient Confidentiality:
    a. Records related to this research study that involve perennial information will only be accessible by the primary research committee and direct assistants. Records will be stored on encrypted, password-protected computer hard drives. A 3-digit code number will be used rather than the subject's name to identify the specific data related to his/her involvement in the study. Only the research investigators will have access to the file that links personal

information to the 3-digit codes, and this file will be stored in a separate location from the actual research data.

Project Timeline:

Item	Date
Study Design; IRB submission (Teresa)	Spring 2016
Background Research	March 2016
Loose conceptual framework	March 2016
Presentation	April 2, 2016
Protocol	May 16, 2016
IRB approval	May 2016
Select study population	August 2016
Clinical Trial	November 2016
Collect Data	January 2017
Research Day Poster	March 2018
Thesis Defense	March 2018
AAO Presentation	April 2018
Manuscript submissions	April 2018

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