

ACCELERATED INVISALIGN® IN CONJUNCTION WITH ACCELEDENT AURA®: A
RANDOMIZED CLINICAL TRIAL

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A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Science in the School of Dentistry (Orthodontics).

Chapel Hill
2018

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ABSTRACT

Brian F. Bragassa: Accelerated Invisalign[®] in conjunction with AcceleDent Aura[®]: A
Randomized Clinical
(Under the direction of Ching-Chang Ko)

Introduction: The objective of our study was to determine if vibration therapy increases the efficiency and accuracy of incisor alignment, accuracy of overbite correction as well as decreases discomfort associated with accelerated (4-day) Invisalign[®]. **Methods:** 33 patients were enrolled in a double-blinded parallel, randomized prospective clinical trial at the UNC Department of Orthodontics. Participants were randomly allocated into one of 3 groups: 2-week aligner wear (G1, n=10), 4-day aligner wear without vibration (G2, n=12) and 4-day aligner wear with vibration (G3, n=11). 3-D virtual models of maxillary and mandibular dentition were captured at 2 different time points: Baseline (T₀) and following 12-weeks of treatment (T_{final}). Efficiency and accuracy of incisor alignment for 63 pre/ post-treatment dental arches was determined by using the percent reduction and percent accuracy of reduction in Proximal Contact Point Discrepancy Index (PCPDI). The accuracy of OB correction was determined for 29 post-treatment models by measuring the percent accuracy of overbite correction (OB). Finally, discomfort and the need for analgesic medication was investigated for each subject at 4 time points (T_{4-days}, T_{2-weeks}, T_{6-weeks}, T_{final}) using a Visual Analog Scale (VAS) and a survey, respectively. **Results:** There was a significant increase in the efficiency of incisor alignment between groups G1 (18.9%) and G3 (29.12%) (P= 0.003). However, there was also a significant decrease in the percent accuracy of incisor alignment between group G1 (48%) and G2

(36%)/G3 subjects (37%)($P=0.023, .047$). There was no significant difference in the percent accuracy of overall OB correction between the 3 groups ($P=0.331, .0664$). However, the percent accuracy of simple OB correction was statistically greater than complex OB correction in within each group ($P=0.039, <0.001, .047$). Pain scores tended to be higher for G2 subjects but the difference was only significant at one time point ($T_{2\text{-weeks}}$) ($P=0.03$). Vibration therapy did not significantly increase the efficiency/accuracy of incisor alignment ($P=0.089, 0.774$) or the accuracy of OB correction ($P=0.33, 0.064$) and decrease the pain associated with accelerated (4-day) Invisalign[®] ($P=0.59, 0.85$). **Conclusion:** Accelerated (4-day) Invisalign[®] increases the efficiency but decreased the accuracy of incisor alignment when compared to a 2-week control group. Simple OB correction is significantly more accurate than complex OB correction when using Invisalign therapy. Vibration therapy has no effect on the efficiency and accuracy of incisor alignment, accuracy of OB correction nor the discomfort associated with accelerated (4-day) Invisalign[®].

ACKNOWLEDGEMENTS

Thank you to my committee members, Dr. Ching-Chang Ko, Dr. Bill Gierie, Dr. Tate Jackson, and Dr. Feng-Chan Lin, for your expertise and direction throughout my project. Thank you to multiple members of Dr. Ko's lab, including: David Lee with digital model measurements and masterful work using Excels spreadsheets. Thank you to undergraduate dental students, Ryan Kearney, Tanner Anderson and Geoffrey Goldsmith for assistance with the intraoral scanner as well as data analysis. Thank you to the Southern Association of Orthodontists for the graciously awarded research grants and OrthoAccel Technology, Inc for donating the AcceleDent Aura[®] devices. Thank you to my classmates and other co-residents. Most of all, thank you to my wife, Michelle, for your support and encouragement of my never-ending studies, all while helping to care for our young family.

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LIST OF ABBREVIATIONS

3-D	Three-Dimensional
OTM	Orthodontic Tooth Movement
OTT	Orthodontic Treatment Time
PCPDI	Proximal Contact Point Discrepancy Index
DAS	Day Aligner Schedule
RCT	Randomized Clinical Trial
OB	Overbite
CAT	Clear Aligner Therapy
ARS	Aligner Reactivation Schedule
RAP	Regional Acceleratory Phenomenon
RANKL	Receptor Activator of Nuclear factor Kappa B Ligand
IL	Interluekin
N	Newtons
KOL	Key Opinion Leader
G	Group
ANOVA	Analysis of Variance
CONSORT	Consolidated Standard of Reporting Trials
B.B.	Brian Bragassa
B.G.	Bill Gierie

LIST OF SYMBOLS

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THE EFFECT OF ACCELEDENT AURA® ON THE EFFICIENCY AND ACCURACY OF INCISOR ALIGNMENT AS WELL AS DISCOMFORT USING ACCELERATED (4-DAY) INVISALIGN®: A RANDOMIZED CLINICAL TRIAL

Introduction

Clear aligners and other advances in orthodontic technology such as ceramic and lingual braces have met the esthetic demands of most orthodontic patients, yet duration of treatment continues to be one of the most challenging aspects of the orthodontic practice.¹ The benefits of accelerated orthodontic treatment are mutually beneficial to both the patient and the orthodontic provider. Reduced treatment time decreases the risk of undesired treatment sequelae (e.g., demineralization, caries and root resorption) for patients. Moreover, orthodontic providers report increased profit margins due to reduced chair time, increased patient satisfaction, and increased organic growth due to differentiation of the practice.¹ Therefore, it is unsurprising treatment efficiency continues to be the focus of orthodontic research as well as development in orthodontic industry.

Historically, orthodontic treatment time (OTT) involves 2 or more years in fixed appliances. However, there is an ever-increasing demand by the public for shorter treatment times.¹ Most parents find 12 to 18 months as an acceptable length of treatment but adolescent patients would prefer less than 6 months.² OTT is determined by severity of the initial malocclusion, age of the patient and the rate of orthodontic tooth movement (OTM), which is determined by the complex cellular process of alveolar bone remodeling.³ Significant advancements in the understanding of bone biology and the mechanism of alveolar bone

remodeling have led to the development of multiple techniques intended to reduce OTT by accelerating the biologic response required for OTM.⁴ According to Uribe, surgical and mechanical/physical techniques can be used to accelerate OTM.¹ Surgical techniques are invasive procedures such as periodontally accelerated osteogenic orthodontics and corticision, which utilize regional acceleratory phenomenon (RAP), or microfractures in the alveolar bone to stimulate osteocyte differentiation and maturation, to increase the rate of OTM.⁵ However, only 11% to 34% of patients are willing to undergo invasive procedures in conjunction with their orthodontic care.¹ Mechanical/physical techniques include: low-level laser therapy, low-level light therapy, and micro-vibration therapy, which the patients use in conjunction with traditional orthodontic care at an additional treatment fee.^{6, 7} The basis for the effects of vibration on accelerating OTM is the stimulation of differentiation and maturation of cells required for alveolar remodeling.³ Therefore, the mechanism for action of vibration therapy appears to be very similar to the effects of more invasive techniques such as corticotomy, or bone perforation.³

Early animal studies and clinical case reports investigating the effects of vibration on OTM yielded promising results.⁸⁻¹⁰ Vibration force applied to *Macaca fuscata* monkeys for 1.5 hours per day over 3 weeks increased tooth movement by 30 percent.⁹ Using a split-mouth design, Leethanakul demonstrated vibrations generated from the head of an electric toothbrush locally increased proinflammatory mediators such as Interleukin (IL)-1 β , which have been linked to increased osteoclastic activity, inflammation, and tooth movement.¹¹ A retrospective clinical study evaluating the rate of alignment and leveling in the mandibular arch of non-extraction subjects reported a 30% increase in the rate of OTM using vibration therapy.¹² According to Nishimura et al., the accelerated OTM resulted from increased RANKL expression in the periodontal ligament. Based on this preliminary data, many orthodontic providers supplemented

traditional orthodontic treatment with vibration therapy as a means to reduce OTT. Also based on the premise that vibration can reduce OTT, 50% to 61% of patients are willing to pay for and undergo treatment with a vibration appliance.¹

In 2009, OrthoAccel Technologies (Houston, TX) introduced AcceleDent[®], a class II medical device scientifically proven to accelerate OTM and reduce OTT. However, a critical review of the literature supporting AcceleDent indicates those studies have low-quality evidence due to poor study design and small sample sizes. Recently conducted prospective clinical trials with favorable study designs and high-quality evidence reported vibration therapy has little effect on the rate of OTM. For example, no difference was noted in the rate of initial alignment in the mandibular arch of non-extraction subjects in a clinical trial using the Tooth Masseur appliance (111 Hz; 0.06 N or about 6g).⁴ Moreover, there was no evidence AcceleDent[®] increased the rate of OTM, or final alignment with fixed appliances in the mandibular arch of patients having mandibular premolars extractions.¹³

Despite a lack of scientific evidence, the AcceleDent Aura[®] device continues to be marketed aggressively by the manufacturer as well as by some orthodontic providers as a means to facilitate accelerated reactivation schedules for clear aligner patients. According to OrthoAccel Technology, Inc. and their supporters, if the AcceleDent Aura[®] device is used in conjunction with clear aligner therapy, OTT can reduce by as much as 50%. This is achieved by increasing the efficacy of aligner treatment and significantly reducing the need for refinement treatment.¹⁴ Orthodontic providers who recommend accelerated aligner schedules in conjunction with vibration therapy report accelerated tooth movement, but further studies are required to determine if vibration therapy is responsible for the reduced OTT. This is especially true with the recent announcement by Align Technologies, Inc. to recommend 7-day aligner wear for all

Invisalign patients without the use of adjunctive therapies. Key opinion leaders, who serve on the North American Clinical Advisory Board for Align Technology, claim significant advancements in Invisalign product innovation including “G-Series” feature, SmartTrack[®] aligner material and clinically proven predictability have allowed the company to confidently recommend one-week wear.¹⁵

Manufacturers of vibration devices also claim daily micro-vibrations can reduce the discomfort associated with orthodontic treatment, but clinical evidence is lacking. One clinical trial conducted by Lobre et al¹⁶ showed micro-pulse vibration significantly reduce the pain scores for overall pain and biting pain during a 4-month evaluation period. Moreover, the same study indicated vibration therapy might be a more effective and safer method of analgesia than using medication. Conversely, however, multiple other high-quality clinical trials have reported little effect of vibration on orthodontic pain and, or quality of life. For example, Woodhouse et al¹⁷ indicated there was no difference in the discomfort experienced, or the consumption of analgesics in patients with fixed appliances. Katchooi et al.¹⁸ determined there was a trend for subjects using vibration in conjunction with 7-day clear aligner therapy (CAT) to report less pain, but the difference was only significant for 1 out 14 time points. In addition to the effect of vibration on treatment pain, the Katchooi et al¹⁸ study also investigated the effect of vibration therapy on the efficacy of treatment associated with accelerated (7-day) CAT. They found 81% of the subjects were able to successfully complete their series of aligners, therefore, it is appropriate to further investigate the effect of vibration on the efficacy of OTM and discomfort associated with accelerated (4-day) CAT. More clinical studies are needed to fully understand the effect of accelerated aligner reactivation schedules (ARS) on the efficiency, efficacy and discomfort associated with CAT.

Therefore, we conducted a prospective randomized clinical trial (RCT) designed to determine the effect of vibration therapy and ARS on the efficiency, efficacy and discomfort associated with accelerated (4-day) CAT. Hopefully, the results of our RCT will provide orthodontic providers with high-quality evidence necessary to make ethical and evidence-based recommendations to patients regarding the effect of vibration as well as ARS on the quality as well as OTT of CAT. Moreover, patients can make an informed decision on whether the potential benefits of vibration and 4-day CAT justify any risks, or additional cost of treatment.

Specific Objectives and Hypotheses

The aims of this RCT are to determine the effect of vibration therapy and a 4- day aligner schedule (DAS) on: (1) the efficiency of upper and lower incisor alignment, (2) accuracy of upper and lower incisor alignment, and (3) the discomfort associated with accelerated (4-day) CAT.

The null hypotheses tested in this study were the following: (1) vibration therapy does not increase the efficiency of upper and lower incisor alignment, (2) vibration therapy will not improve the accuracy of upper and lower incisor alignment, and (3) vibration therapy does not decrease the discomfort associated with accelerated (4-day) CAT.

Material and Methods:

Trial design and any changes after trial commencement

This study was designed as a double blinded, single-centered 3-arm, parallel, prospective randomized clinical trial with 1:1:1 allocation ratio.

Participants, eligibility criteria and settings

Ethical approval was granted by the Office of Human Research Ethics at the University of North Carolina (reference number: 16-0167). The clinical trial was registered at the US

National Institutes of Health (ClinicalTrials.gov) #NC NCT02868554. See CONSORT flow diagram (Figure 2).

The study population was drawn from patients pursuing Invisalign[®] treatment in the postgraduate orthodontic clinic of the University of North Carolina (UNC). Patients were included for participation based on the following criteria: (1) being within the ages of 18-65 years old, (2) good health determined by a current medical history, (3) full adult dentition including second molars in both dental arches, (4) normal pulp vitality and healthy periodontal tissues as determined by intraoral exam, (5) initial malocclusion with mild to moderate dental crowding or spacing ($\leq 6\text{mm}$), (6) non-extraction Invisalign treatment with ClinCheck treatment plans prescribing more than 21 active aligners with simultaneous tooth movement of anterior teeth and no deviation from default amounts of tooth movements prescribed in each aligner stage, (7) no mid-course correction, or additional aligners, and (8) willingness to and ability to comply with study procedures, attend study visits, and complete the study protocol.

Patients were excluded from participation based on the following criteria: (1) individuals diagnosed with systemic diseases such as diabetes, hypertension, temporomandibular disorders, or cranio-facial syndromes, (2) chronic use of any non-steroidal anti-inflammatory medications, estrogen, calcitonin, or corticosteroids, (3) history of use or current use of bisphosphonate medication or other medication for treatment of osteoporosis, (4) current smoker (not within the last 6 months), (5) significant periodontal disease ($>4\text{mm}$ pocket depth or $>2\text{mm}$ recession), (5) active caries, or new dental restorations during treatment (6) initial malocclusions with severe crowding or spacing ($>6\text{mm}$), (7) impacted teeth and, or closure of extraction spaces, requiring fixed appliances or adjunctive procedures other than clear aligners, (8) ClinCheck treatment

plans with less than 21 aligners, or plans that failed to start all tooth movement simultaneously, and finally, (9) failing to comply with research protocols.

Enrolled subjects were allocated into one of 3 groups: 14-DAS (control- G1), 4-DAS (G2), and 4-DAS plus vibration therapy using AcceleDent Aura[®] (G3). Informed consent and assent were obtained prior to initiating the clinical trial protocol. In total 67 patients were screened for eligibility, 34 patients were excluded for not meeting the previously mentioned criteria, and 33 patients were enrolled under the supervision of Dr. Bill Gierie, who is an Elite top 1% Invisalign provider and also serves as a KOL for Invisalign. Dr. Gierie was blinded to group allocation of all subjects during the initial set-up and approval of the ClinCheck treatment plan, however, he was made aware if the patient was in the study to ensure no additional modifications were requested to alter the rate of programmed tooth movement per aligner (0.25mm/aligner). Once the aligners arrived from the manufacture, enrolled patients were scheduled for aligner delivery and randomly allocated to one of the 3 groups using third party randomization software.

According to group allocation and Invisalign[®] start date (To), customized aligner schedules were issued to all subjects and recall appointments were scheduled for data acquisition. Subjects in the control group (G1) were instructed to wear each aligner set 14 days. Subjects receiving an accelerated aligner schedule (G2/G3) were instructed to wear each aligner set 4 days. All subjects were instructed to wear each aligner at least 22 hours per day and progress to the subsequent aligner based upon their customized schedule. Subjects receiving vibration therapy (G3) were issued a fully charged AcceleDent Aura[®] device with operating instructions and compliance counseling. Vibration therapy was applied for 20 minutes per day at a force of .25N (25g) at a frequency of 30Hz. G3 subjects were blinded from the fact that the AcceleDent Aura device contains Fastrac[®] software which is a microprocessor that stores the date

and duration of use each time the device was activated. All subjects were recalled at the following time points for data collection: T_{4-days}, T_{2-weeks}, T_{6-weeks}, and T_{12-weeks} after the Invisalign start date.

The investigator completed the following research steps at each recall visit: (1) obtain virtual models of maxillary and mandibular dental arches using Trios 3Shape scanner and (2) determine discomfort experienced by the subject at the onset of subsequent aligner delivery using the Faces Pain Scale[®]. Subjects were also asked to indicate the number of hours they typically wear the Invisalign trays and if analgesics were used to relieve discomfort associated with their treatment.

Under faculty supervision, orthodontic residents completed the following clinical steps specific to each recall visit: (T₀)[a] deliver aligner #1, (T_{4-days}) [a] deliver aligner #s: 2-4 to G2/G3 subjects only, (T_{2-weeks}) [a] place composite attachments prescribed in the ClinCheck treatment plan and [b] deliver aligner #s: 2-3 to G1 subjects and aligner #s: 5-11 to G2/G3 subjects, (T_{6-weeks}) [a] deliver aligner #s: 4-6 to G1 subjects and aligner #s: 12-21 to G2/G3 subjects, (T_{12-weeks}) [a] terminate study protocol and continue treatment under the guidance of attending faculty, Dr. Bill Gierie.

Outcomes (primary, secondary and tertiary) and any changes after the trial commencement

The primary outcome measure within the three groups was the percent reduction in Proximal Contact Point Discrepancy Index (PCPDI), which involves measuring the linear displacement of the anatomical contact of each incisor from the adjacent tooth anatomic point, the sum of these displacements representing the relative degree of anterior irregularity (Figure 1). Perfect alignment from the mesial aspect of the left canine to right canine would theoretically have a score of 0.¹⁹ For each subject at baseline (T₀) and following 12-weeks of treatment (T₁₂₋

weeks), the PCPDI was determined separately for maxillary (#s: 6-11) and mandibular (#s: 22-27) anterior teeth on digital study models (.stl) captured with intra-oral scans. The percent reduction in PCPDI was determined with the following equation: % reduction PCPDI 100%: $[(|initial\ PCPDI - achieved\ PCPDI| / initial\ PCPDI) * 100]$.

The secondary outcome measure, within each group, was the percent accuracy of PCPDI reduction, which was defined by the following equation: % accuracy PCDP reduction $[(|initial\ PCPDI - achieved\ PCPDI|) / (|initial\ PCPDI - goal\ PCPDI|) * 100]$. Again, because in our study only reflected outcomes following the initial 12 weeks of treatment, the goal PCPDI for our subjects was determined as a percentage of the total predicted PCPDI correction (G1= 6 aligners/ total # aligners/ G2&G3= 21 aligners/ total # of aligners). For example, the equation for goal PCPDI in control group subjects (G1) was: $[(|initial\ PCPDI - predicted\ PCPDI|) \times |6\ aligners / total\ \#\ of\ active\ aligners|]$. Calculating the accuracy of the percent reduction in PCPDI was necessary to overcome the discrepancy of number of aligners completed within each group during the 12 weeks study.

The tertiary outcome measurement, as determined by the subjects within each group, was the mean (%) pain score associated with the onset of each aligner set. Pain scores were collected using a numerical analog scale (Pain Faces Scale[®], 0 {no pain}- 10 {severe pain}), which allowed subjects to rate the discomfort associated with inserting the each subsequent aligner. In addition to pain scores, subjects indicated, yes (Y=1), or no (N=0), if analgesics were used to relieve discomfort associated with their treatment.

Finally, daily compliance using the AcceleDent Aura[®] device as well as the Invisalign trays was monitored throughout the study. Compliance with the vibration device was measured using the OrthoAccel, Inc. proprietary software, FastTrac[®]. All subjects were advised to wear the

Invisalign trays 20-22 hours per day and compliance pertaining to use of the Invisalign trays was self-reported using a questionnaire. Survey data was collected at each recall visit: T₀, T_{4-days}, T_{2-weeks}, T_{6-weeks}, and T_{12-weeks}.

To obtain the T₀, T_{12-weeks} and goal PCPDI measurements, we imported final ClinCheck models (.stl) as well as the intra-oral digital study models (.stl) into Geomagic DesignX64 software. For each digital model at each time point, a single blinded investigator (B.B) reproducibly selected the proximal contact points of maxillary and mandibular incisors.

Sample size calculation

The main outcome measure in this study was the (1) percent reduction in PCPDI during the initial 12-weeks of treatment. Sample size estimation was completed using G*Power 3.1 software and showed a total of 21 participants (42 dental arches), 7 participants (14 dental arches) in each treatment arm, was required to demonstrate a clinically significant difference in the primary outcome of a 75% increase in the rate of incisor alignment between G1 and G2/G3, with 80% power, a standard deviation of 0.1, and an alpha of 0.05, using two sample T-test, and with the null hypothesis of equal effect. In addition, to allow for a potential 30% dropout rate, the sample size was increased to 30 subjects.

Interim analyses and stopping of guidelines

No intervention analysis was performed during the study. During the design of study protocol, we decided the trial would be stopped if any harm came as a result of the interventions.

Randomization

An independent, third party biostatistician, using an electronic program, R 3.4.2, completed randomization of the subject allocation sequence. All subjects enrolled within the study were randomized in blocks of 6 to the 3 groups that correspond to one of the 3 treatment

options to be studied. Allocation concealment was secured by contacting the sequence generator for assignment. 10 subjects were randomized to the 14-DAS (G1), 12 subjects were randomized to the 4-DAS (G2), and 11 subjects were randomized to the 4-DAS plus vibration therapy (G3). All subjects enrolled within the study (33) received an allocation intervention.

Blinding

Blinding of either the patient, or the assigned orthodontic resident, was not possible during this clinical trial due to a lack of sham vibration devices. It was also the opinion of the investigator that a sham device was not a realistic way of eliminating the placebo effect, which has been repeatedly discussed in previous studies evaluating pain scores. However, the part-time faculty member (B.G.) was blinded during the initial set-up of the ClinCheck treatment plans and the research investigator (B.B.) was blinded during data analysis. The digital models used to perform the PCPDI measurements were de-identified and assigned a three-digit code to ensure the investigator was unaware of the patient's intervention method.

Statistical Analysis

Descriptive statistics on demographic, clinical characteristics, and outcomes Invisalign treatment were calculated. Since a large correlation coefficient (0.25) was present between upper and lower teeth in the percent reduction of PCPDI, repeated measures ANOVA was used as the primary statistical method to account for the dependence. A categorical variable with 3 levels was created for the group in the linear mixed effects model with a random intercept. The statistical significance of the difference between groups in both primary and secondary outcomes was tested using a t-test obtained from the parameter estimation. Since there is no significant difference in baseline characteristics, we did not adjust for any covariates in the mixed effects

model. P-values less than 0.05 were considered statistically significant. All of the statistical analyses were implemented using SAS 9.4 (Cary, NC).

Compliance data downloaded from the devices were analyzed. The difference the primary, secondary and tertiary aims between compliers and non-compliers were measured using the Wilcoxon rank sum test. Self-reported aligner compliance data, pain level on the numeric scale and the need for analgesic medication data were gathered from the subject surveys and analyzed. We will use Wilcoxon rank sum test to measure the differences between the arms of the study.

Results:

Participant Flow

Open enrollment began in May 2016 and continued until November 2017. 33 subjects (mean age, 32.3yrs; SD: 9.21; max: 57yrs; min: 18yrs) were randomized to one of 3 intervention groups: 14-day aligner schedule (G1), 4-day aligner schedule (G2), and 4-day aligner schedule + vibration therapy (G3). Data from 2 subjects (2 maxillary arches and 1 mandibular arch) were eliminated from the data sample prior to analysis because the ClinCheck[®] treatment plans did not initiate tooth movement simultaneously. This resulted in the final analysis of 63 dental arches (31 maxillary and 32 mandibular). The recruitment and follow-up of all subjects during the study is shown in the CONSORT flow diagram (Figure 2). No subject was lost to follow-up during this study.

Baseline Data

Table 1 shows the similarity in the distributions across treatment groups for demographic, initial PCPDI for maxillary and mandibular dentition as well as the average number of aligners

used per group. Table 2 displays the mean self-reported aligner use per day within each group. Figure 3 illustrates the compliance with the AcceleDent Aura[®] by subjects within G3.

Numbers analyzed for the primary aim (percent reduction in proximal contact point discrepancy index)

Our results indicated a statistically significant difference in the percent reduction of the PCPDI between the control group (G1-18.9%) and the accelerated Invisalign in conjunction with vibration group (G3-29.1%) ($P=0.003$). However, no statistically significant difference was found between the control group (G1) and the accelerated Invisalign group (G2- 23.8%) ($P=0.125$) nor the accelerated Invisalign group (G2) and the accelerated Invisalign in conjunction with vibration group (G3) ($P=0.089$) (Figure 4). These results were not altered after adjusting for the various confounding factors.

Compliance was found to drop-off markedly during the period of the trial. Only 6 participants (54%) met the criterion of being considered compliant by using the vibration device 75% of the time or more (Figure 3). The mean percent reduction of PCPDI in the compliant subjects was 27.9% while non-compliant subjects had a 31.6% reduction, thus, showing vibration therapy had little effect on the efficiency of incisor alignment. The mean compliance with aligner use was within recommended range (20.9 hours per day) and the means of use within the groups was not statistically different (Table 3)

Numbers analyzed for the secondary aim (% accuracy of incisor alignment)

There was a statistically significant difference in the mean accuracy of PCPDI reduction (%) between the control group (G1- 48.3%) and the accelerated Invisalign group (G2- 36.1%)($P=0.0235$) as well as the accelerated Invisalign in conjunction with vibration group (G3- 37.7%) ($P=0.047$). However, no statistically significant difference was found when evaluating

the effect of vibration between G2 and G3 ($P=0.284$). These results were not altered after adjusting for the various confounding factors. (Figure 5)

Compliance with the vibration device was found to drop-off markedly during the period of the trial. Only 6 participants (54%) met the criterion of being considered as good compliers by using the vibration device 75% of the time or more (Figure 3). The mean accuracy of PCPDI reduction in compliant subjects was 38.2% while the non-compliant subjects had a 37.3% reduction, thus, showing vibration therapy had little effect on the accuracy of incisor alignment. The mean compliance with aligner use was within recommended range (20.9 hours per day) and the means of use within the groups was not statistically different (Table 3)

Numbers analyzed for tertiary aim (Pain scores and analgesic consumption)

When comparing mean pain scores in each group by time point, the only significant difference occurred at $T_{2\text{-weeks}}$, where G2 subjects experienced significantly more discomfort than G1 subjects ($P= 0.033$). (Figure 6) The mean pain scores decreased significantly by time point throughout the 12 week study period ($P= 0.005$). When investigating the consumption of analgesics, there was no statistically significant difference between the groups ($P= 0.612$). Analgesic medication consumption was the highest at T1 for all groups (G1-14%, G2- 17%, G3- 27%). (Figure 7)

Error of the Method

To reduce effects of random measurement error and calculate intra-operator reliability, the same single operator (B.B) manually repeated the steps to measure the PCPDI measurements 3 times and allowed 1-weeks time to pass between measurements. The accepted PCPDI value used to calculate the percent reduction and accuracy of PCPDI correction was the average of 3

completed measurements. The Dahlberg²⁰ measurement error calculations showed a 0.1mm difference between the initial and repeated measures.

Harms

There was no evidence of adverse events, or safety hazards, to the soft or hard tissues of the participants during the trial.

Discussion:

Main findings in the context of the existing evidence, interpretation

Given the substantial growth of clear aligners within the orthodontic market and the increasing demand for reduced treatment time, there is a substantial need to clearly understand the factors contributing to OTT when using CAT. Orthodontic providers need high quality evidence to base their treatment recommendations on and to help avoid potential liabilities associated with accelerated orthodontic treatment.²¹ Patients should not be misled by the aggressive marketing strategies of orthodontic manufacturers, or orthodontic providers attempting to differentiate their practice from competitors with false claims of accelerated treatment.

Despite significant advancements in the understanding of bone biology, OTT continues to be limited by the rate of OTM, which is further affected by case complexity and the age of the patient. Several invasive and non-invasive techniques have been developed as means of accelerating the intricate cellular pathways involved with alveolar bone remodeling.¹ Although a few published scientific and clinical studies indicate vibration can accelerate OTM, the clinical significance of the benefits resulting from vibration therapy remains in question.

In this RCT, we evaluated the effects of accelerated (4-day) CAT and vibration therapy on the efficiency and accuracy of upper and lower incisor alignment. The demographics of our

study sample were 64% female, however, this reflects a “real-world” scenario as females are generally more concerned with esthetics and duration of treatment.²² The average of age was similar between allocation groups (32.3yrs, SD: 9.85). Additionally, there was no difference in the characteristics of the initial malocclusions between the groups and the mean number of aligners (G1-30.5, G2-32.3 and G3-32.6). Thus, our study sample was ideal for determining the aims of our study.

When evaluating the efficiency of incisor alignment, which again was the percent reduction in PCPDI, between the 3 groups, we noted a trend for the accelerated groups (G2/G3) to be more efficient than G1, which seems logical because subjects in G2 and G3 completed 21 aligners versus the 6 aligners completed by G1 subjects. The only significant difference was noted between G3 subjects and G1 subjects which means the effect of a 4-day aligner schedule plus vibration was more efficient than the 2-week control group. However, because there was not a significant difference between G2 and G3 subjects, we can conclude vibration had no effect on the efficiency of incisor alignment. These results agree with multiple previously conducted prospective RCTs, which indicated the effect of vibration on the rate of OTM is negligible.^{13,23,18}

To more thoroughly understand the effect of vibration therapy on accuracy of accelerated (4-day) CAT, we compared the accuracy of achieved percent reduction in PCPDI to the predicted reduction in PCPDI within each group. Our results indicated G1 subjects achieved 25% more of the predicted incisor alignment than G2 and G3 subjects. The effect of vibration resulted in a slight increase (3%) in the accuracy of the achieved incisor alignment, but the impact was not significant. When comparing our study recently published by Katchooi et al²⁴, who reported 65% accuracy of incisor alignment using 7-DASs \pm vibration, our results indicate 4-DASs \pm vibration exacerbate the accuracy of incisor alignment.

Our results indicate mean pain scores were low overall ($<2.5/10$) and mean pain scores significantly decrease over the course of treatment. Our results indicated a trend that G1 and G3 subjects may have experienced less pain than G2 subjects but the difference was only significant at the 2-week follow up appointment. Vibration seemed to reduce some of the pain experienced between G2 and G3 subject, although the difference was not significant. This result was very similar to the findings published recently by Katchooi et al¹⁸, who compared pain levels associated of 7-day ARS with a 2-week CAT protocol. Additionally, our findings showed there was no difference in consumption of analgesic medication between the groups, but it was interesting to note our subjects only used pain medication following delivery of the initial aligner and mean pain scores were similar to those reported by Katchooi et al²⁴. Perhaps the most interesting finding from our pain data was that G2 subjects consumed less pain medication than G3 subjects. This finding may provide some explanation of why G3 subjects experienced less pain than G2 subjects. If vibration did, in fact, play a role in reducing discomfort associated with treatment, the effect was undoubtedly not clinically significant.

Similar to previously published studies evaluating the effect of vibration therapy, our subjects demonstrated poor compliance using the AcceleDent Aura device. According to the AcceleDent Fastrac[®] usage reports collected in our study, only 6 of the 11 (54%) G3 subjects used the device as directed by the manufacturer more than 75% of the days. However, there was no significant difference in the accuracy of incisor alignment between compliant and non-compliant subjects (38% and 37%, respectively). The poor compliance noted in our study is reflective of a real-world orthodontic practice; therefore, all AcceleDent users were examined in determining the effect of vibration therapy.

Interpretation of our results indicates accelerated (4-day) Invisalign can increase the efficiency of incisor alignment without significantly more discomfort when compared to 2-week or 7-day regimens. However, our study also reveals the side effect of increased efficiency is a significant reduction in the accuracy of desired incisor alignment. Our study revealed trends leading to the possibility of vibration therapy having a positive effect on efficiency and efficacy of accelerated CAT, but the difference was not statistically significant within our relatively small sample size. The majority of improved efficiency noted in the accelerated groups resulted from the 4-DAS. One could argue that with a larger sample size, or improved compliance using the vibration device, the difference in the efficiency between groups G2 and G3 may have been statistically significant, but the clinical significance would undoubtedly remain trivial.

In terms of OTT with CAT, we cannot definitively conclude overall treatment time will be reduced because of the accuracy of accelerated CAT is significantly reduced. Orthodontic providers and patients using accelerated (4-day) aligner schedules may require more mid-course corrections, or refinements, to achieve the desired result of treatment. Even if significant compensations are made in the ClinCheck treatment plan as a means to overcome the side effects of 4-DAS, OTT will not, necessarily, be reduced because more aligners will be required to achieve the same desired outcome. Increasing the number of aligners may contribute to patient burn out, which often leads to poor compliance and potentially, a negative overall experience with treatment.¹⁸

The choice of using accelerated ARSs with, or without, vibration as an adjunctive therapy to accelerate OTM and potentially reduce OTT will continue to be at the discretion of the orthodontic provider and patient. However, the results of this study provide scientific evidence to help providers make more informed treatment recommendation for which they are liable. More

long-term clinical studies with larger sample sizes and are needed to fully understand the effect of vibration and accelerated ARSs on the efficiency and accuracy of CAT. The ideal time regimen for each aligner set likely varies based on the initial malocclusion and treatment outcomes desired by the patient.

Limitations

Clinical studies that provide good-quality patient care while testing alternative treatments must, by their very nature, involve compromises. One limitation of our study was not blinding the research subjects to their intervention group. However, significant patient blinding was impossible, while maintaining the clinical applicability of the study. Previous studies have used sham vibration devices, but with questionable efficacy in regards to blinding. The absence of blinding of our subjects most likely affected the pain scores reported within each group due to the presence of, or lack of, placebo effect. The results of our study were also subject to the potential for poor patient compliance with the Invisalign, or vibration device. Although patients reported acceptable levels of compliance wearing Invisalign trays, we were unable to verify the daily frequency of aligner use for each patient. Additionally, we do not know the short versus long-term effects of vibration therapy on OTM, but the short (12-week) evaluation period in this trial may not have allowed for the cumulative affect of vibration therapy. Finally, the effect of bite force on the vibration device mouthpiece may have affected the results of our study.

Generalizability

The demographics and clinical characteristics associated with our research subjects are representative of the adult population currently seeking orthodontic treatment and are concerned with the issues of esthetics and duration of treatment. The results and conclusions made from our study have generalizability only to the efficiency and accuracy as well as discomfort associated

with the alignment maxillary and mandibular incisor when using accelerated (4-day) Invisalign. The challenges we experienced related to patient compliance wearing the aligners and using the vibration device reflect real-world issues common throughout all orthodontic treatment outside of a research setting.

Conclusions:

1. Accelerated (4-day) aligner wear increases efficiency but decreases accuracy of incisor alignment
2. Overall treatment time using accelerated (4-day) aligner schedules may be increased due to need for future refinement
3. Vibration had no effect of efficiency and accuracy of incisor alignment nor the discomfort associated with accelerated (4-day) Invisalign
4. Further clinical trials with larger sample sizes are required to further determine:
 - a. The ideal aligner reactivation schedule in order to maximize the efficiency and accuracy of clear aligner therapy in various types of malocclusions.

Table 1. Baseline characteristics by treatment group

		Group 1		Group 2		Group 3		Total		P- value
		n	%	n	%	n	%	n	%	G1 vs G2, G1 vs G3, G2 vs G3
Sex										
	Male	5	50	3	25	4	36	9	36	
	Female	5	50	9	75	7	64	19	64	
Age (y) (mean \pm SD)		35.5 \pm 10.45		31.25 \pm 9.25		30.33 \pm 7.95		32.36 \pm 9.21		0.54, 0.45, 0.66
Initial maxillary incisor PCPDI (mean \pm SD)		4.01 \pm 1.22		4.22 \pm 2.05		4.75 \pm 1.30		4.33 \pm 1.85		0.77, 0.54, 0.76
Initial mandibular incisor PCPDI (mean \pm SD)		4.15 \pm 2.29		4.58 \pm 1.82		4.65 \pm 1.19		4.46 \pm 1.42		0.65, 0.35, 0.33
Number of aligners (mean)		30.55 \pm 6.99		32.3 \pm 8.05		32.6 \pm 7.04		31.8 \pm 7.23		0.23, 0.34, 0.45

Table 2: Self-reported aligner use in hours per day

		Group 1	Group 2	Group 3	Total	P-value
T1						
	n	7	12	10	29	
	Mean	22.6	20.6	23.1	22.1	0.89
	SD	1.8	1.7	1.4	1.63	
T2						
	n	7	12	10	29	
	Mean	20.6	20.1	22.8	21.167	0.72
	SD	1.5	1.3	1.8	1.53	
T3						
	n	7	12	10	29	
	Mean	20.3	19.7	21.7	20.56	0.75
	SD	1.8	1.5	1.9	1.73	
Tfinal						
	n	7	12	10	29	
	Mean	20.2	19.5	20.8	20.16	0.56
	SD	1.7	1.9	2	1.86	

Figure 1: Digital pre-treatment and post-treatment dental models (.stl files) used for calculating the Proximal Contact point Discrepancy Index (PCPDI).

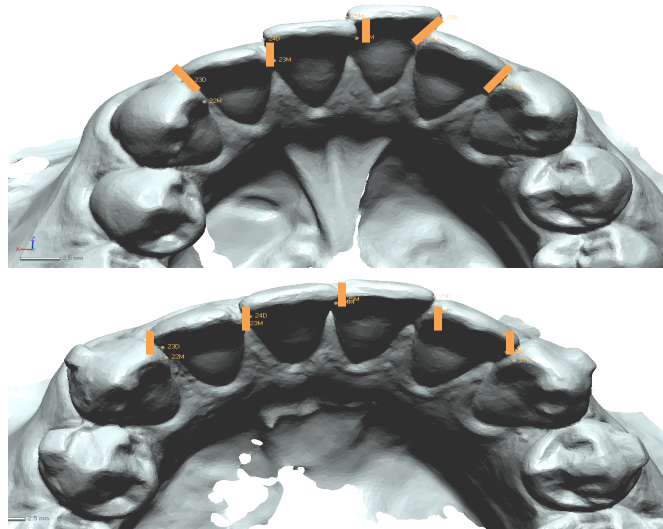


Figure 2: CONSORT diagram showing the flow of subjects in the study

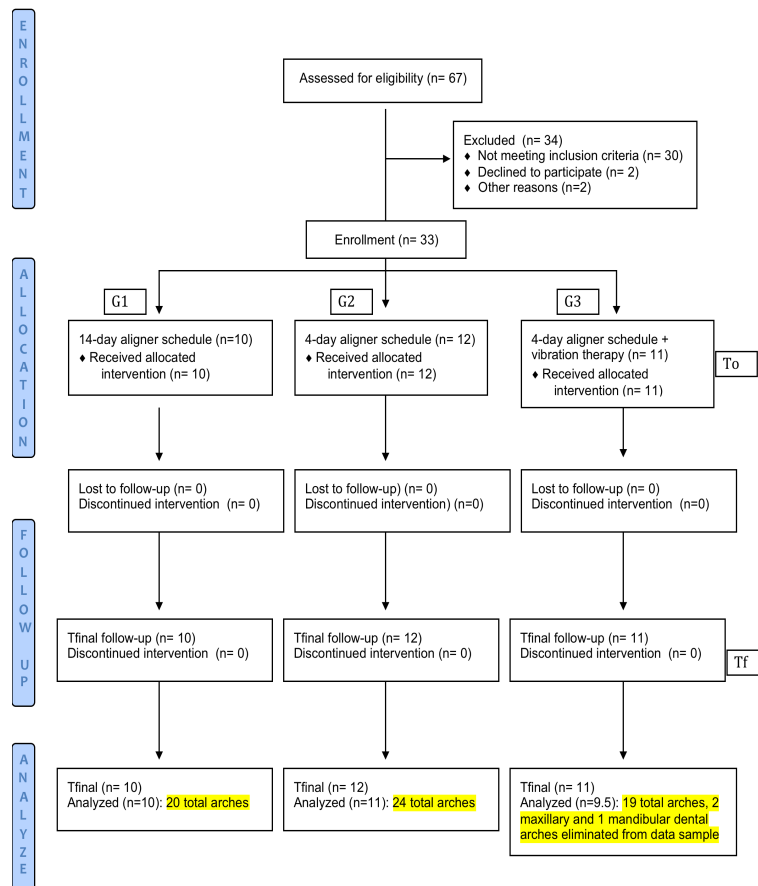


Figure 3. Percentage of G3 subjects compliant with the AcceleDent Aura device in 12 weeks

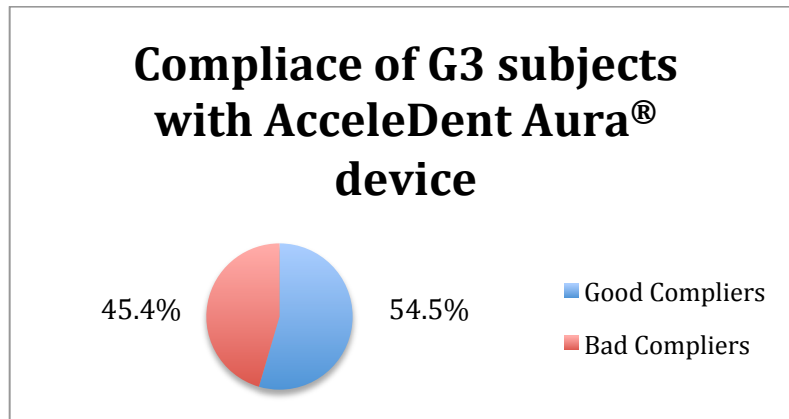


Figure 4. Efficiency of incisor alignment in 12 weeks

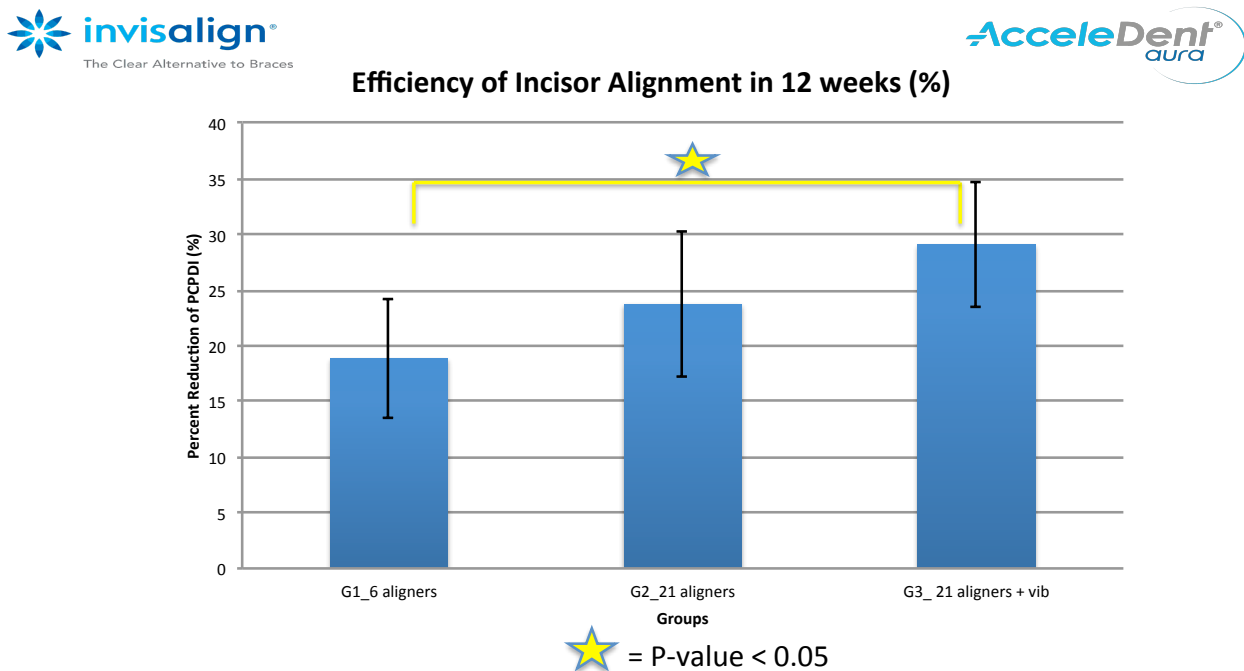


Figure 5. Accuracy of incisor alignment in 12 weeks

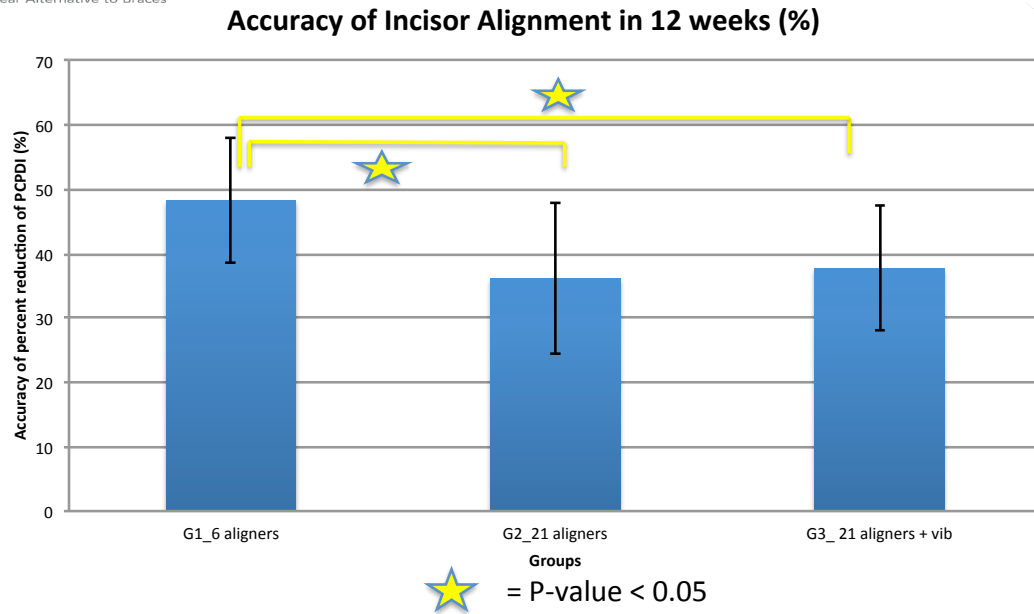


Figure 6. Mean pain scores by group and time point

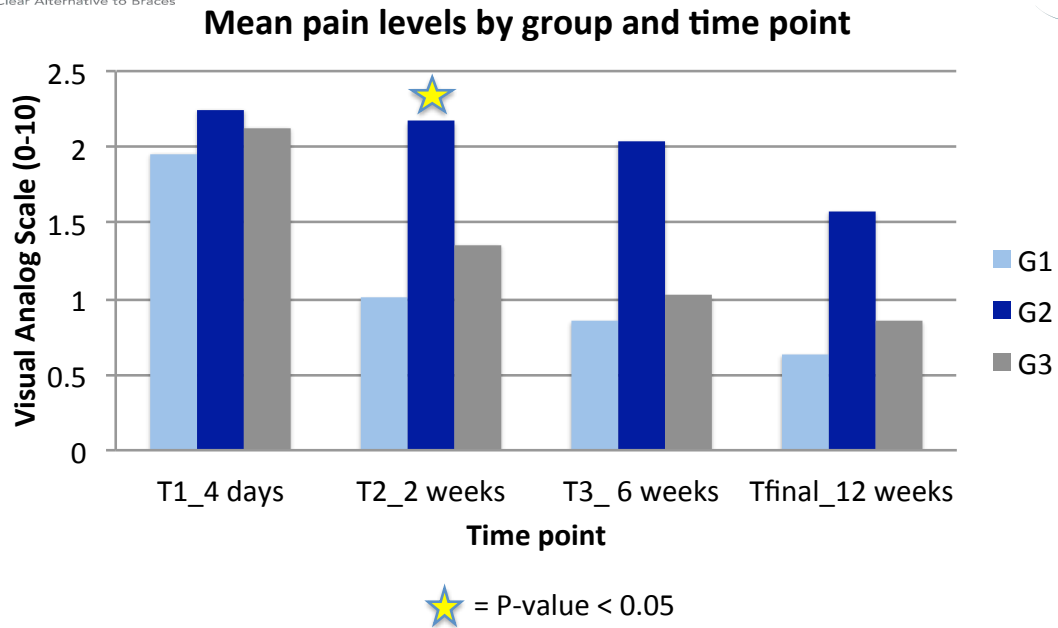
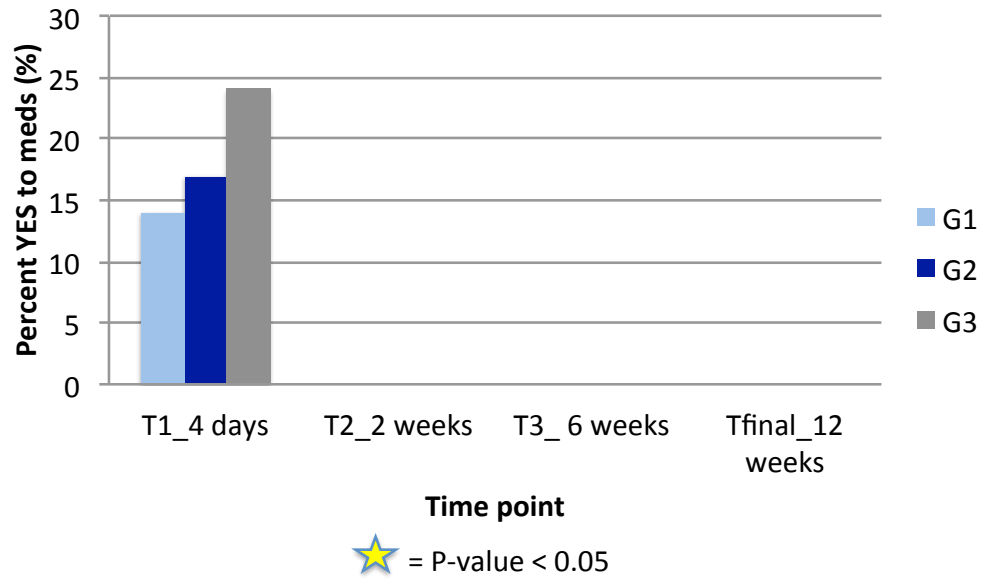


Figure 7. Mean Analgesic Consumption by group and time point



Analgesic medication by group and time point



REFERENCES

1. Uribe F, Padala S, Allareddy V, Nanda R. Patients', parents', and orthodontists' perceptions of the need for and costs of additional procedures to reduce treatment time. *Am J Orthod Dentofac Orthop*. 2014;145(4 SUPPL.):S65-S73. doi:10.1016/j.ajodo.2013.12.015
2. Fink DF, Smith RJ. The duration of orthodontic treatment. *Am J Orthod Dentofac Orthop*. 1992;102(1):45-51. doi:10.1016/0889-5406(92)70013-Z
3. Proff P, Römer P. The molecular mechanism behind bone remodelling: A review. *Clin Oral Investig*. 2009;13(4):355-362. doi:10.1007/s00784-009-0268-2
4. Miles, Peter, H Smith, R Weyant DR. The effects of a vibrational appliance on tooth movement and patient discomfort: a prospective randomised clinical trial. *Am J Orthod Dentofac Orthop*. 2012;28(2):213-218.
5. Wilcko, Thomas, M. Wilcko, William, Bissada N. An Evidence-Based Analysis of Periodontally Accelerated Orthodontic and Osteogenic Techniques: A Synthesis of Scientific Perspectives. *Semin Orthod*. 2008;14:305-316.
6. Youssef M. The effect of low-level laser therapy during orthodontic movement: a preliminary study. *Lasers Med Sci*. 2008;23(1):27-33.
7. Kau, CH; Kantarci, A; Shaughnessy, T; Vachiramon, A, Santiwog, P et al. Photobiomodulation accelerates orthodontic alignment in the early phase of treatment. *Progress Orthod*. 2013;14(1):30.
8. Darendeliler MA. Effects of pulsed electromagnetic field vibration on tooth movement induced by magnetic and mechanical forces: a preliminary study. *Aust Dent J*. 2007;52(4):282-287.
9. Shimizu Y. Movement of the lateral incisors in *Macaca fuscata* as loaded by a vibrating force]. 1986;45(1):56-72.
10. Nishimura M, Chiba M, Ohashi T, et al. Periodontal tissue activation by vibration: Intermittent stimulation by resonance vibration accelerates experimental tooth movement in rats. *Am J Orthod Dentofac Orthop*. 2008;133(4):572-583. doi:10.1016/j.ajodo.2006.01.046
11. Leethanakul C, Suamphan S, Jitpukdeebodintr S, Thongudomporn U, Charoemratrote C. Vibratory stimulation increases interleukin-1 beta secretion during orthodontic tooth movement. *Angle Orthod*. 2016;86(1):74-80. doi:10.2319/111914-830.1
12. Bowman SJ. The effect of vibration on the rate of leveling and alignment. *J Clin Orthod*. 2014;48(11):678-688.

13. Woodhouse NR, Dibiasi AT, Johnson N, et al. Supplemental vibrational force during orthodontic alignment: A randomized trial. *J Dent Res*. 2015;94(5):682-689. doi:10.1177/0022034515576195
14. AcceleDent.com.
15. Technology A. ALIGN TECHNOLOGY INTRODUCES ONE-WEEK ALIGNER WEAR FOR INVISALIGN(R) TEEN AND FULL PRODUCTS.
16. Lobre WD, Callegari BJ, Gardner G, Marsh CM, Bush AC, Dunn WJ. Pain control in orthodontics using a micropulse vibration device: A randomized clinical trial. *Angle Orthod*. 2016;86(4):625-630. doi:10.2319/072115-492.1
17. Woodhouse NR, Dibiasi AT, Papageorgiou SN, et al. Supplemental vibrational force does not reduce pain experience during initial alignment with fixed orthodontic appliances: A multicenter randomized clinical trial. *Sci Rep*. 2015;5(September):1-9. doi:10.1038/srep17224
18. Katchooi, Mina; Cohanin, Bobby et. al. Effect of supplemental vibration on orthodontic treatment with aligners: A randomized trial. *Am J Orthod Dentofac Orthop*. 2018;153:336-346.
19. Tran AM, Rugh JD, Chacon JA, Hatch JP. Reliability and validity of a computer-based Little irregularity index. *Am J Orthod Dentofac Orthop*. 2003;123(3):349-351. doi:10.1067/mod.2003.76
20. Dahlberg G. Statistical methods for medical and biological students. *New York Intersci Publ*. 1940.
21. Laurance J. Accelerated orthodontics or accelerated liability? *Am J Orthod Dentofac Orthop*. 2014;145(4):148-151.
22. Walton DK, Fields HW, Johnston WM, Rosenstiel SF, Firestone AR, Christensen JC. Orthodontic appliance preferences of children and adolescents. *Am J Orthod Dentofac Orthop*. 2010;138(6). doi:10.1016/j.ajodo.2010.06.012
23. Miles P, Fisher E. Assessment of the changes in arch perimeter and irregularity in the mandibular arch during initial a. *Am J Orthod Dentofac Orthop*. 2016;150(1):928-936.
24. Katchooi, Mina; Cohanin, Bobby, Tai S. Effect of supplemental vibration on orthodontic treatment with aligners: A randomized trial. *Am J Orthod Dentofac Orthop*. 2018;153:336-346.

THE EFFECT OF ACCELEDENT AURA ON THE ACCURACY OF OVERBITE CORRECTION WHEN USING ACCELERATED (4-DAY) INVISALIGN®: AN EXPLORTIVE RANDOMIZED CLINICAL TRIAL

Introduction:

The goal of orthodontic treatment is to produce an ideal occlusion that is morphologically stable, esthetic, and functional.¹ However, the orthodontic market has recently experienced a paradigm shift towards an increased demand for consumer-driven esthetic treatment as well as a reduction in treatment time.² Recent computer based surveys indicate adults and teenagers rate clear aligners as the most esthetic and acceptable appliance for orthodontics treatment.³ Align Technology (eg Invisalign®, Santa Clara, CA, USA) has met the esthetic demands of the public, however, orthodontic treatment time (OTT) using Invisalign® continues to be investigated.

In addition to the traditional factors affecting duration of treatment⁴, OTT with clear aligner therapy (CAT) is further affected by: total number of aligners, rate of orthodontic tooth movement (OTM) programmed in each aligner, aligner reactivation schedule (ARS), and finally, the accuracy of treatment. The total number of aligners is determined by the severity of the initial malocclusion as well as the staging of OTM, which is influenced by the most complex tooth movement required for a single tooth, or group of teeth. The rate of OTM is determined by the manufacturer and reflects the maximum amount of linear (0.25mm), or angular (2 deg), movement a single tooth, or a small group of teeth, programmed within each aligner. Orthodontic providers cannot increase the default rates of OTM per aligner, but distributing the desired tooth movement over a larger number of aligners can reduce the rate of OTM. Reducing

the rate of OTM per aligner may be necessary to improve the accuracy of some complex tooth movement.⁵

The aligner reactivation schedule (ARS) is defined as the number of days each aligner set is worn by the patient. ARS is critical because adequate time must be given to achieve the tooth movements programmed within each aligner, however, there is very little clinical evidence to support the most ideal regimen in terms of efficiency and accuracy of specific types of OTM. Historically, Align Technology, Inc. recommended 2-week ARSs as well as a daily use requirement of 20-22 hours, however, in October of 2016, the manufacturer deviated from the standard 2-week change regimen and introduced 1-week aligner wear for all Invisalign patients without adjunctive therapies like vibration. Align Technology, Inc. claims the recent change in ARS comes as a result of continued Invisalign product innovation including the “G-Series” features and SmartTrack[®] aligner material. Align Technology also states their recommendation is based on clinical analysis of more than 200 in-progress Invisalign cases, the experiences of numerous Invisalign providers, and the endorsement of the North American Clinical Advisory Board.⁶

Despite the recommendation of Align’s Key Opinion Leaders, there is reasonable concern the recent announcement is in response to the ever-increasing demand for reduced treatment times. Factors such as: type of malocclusion, patient compliance as well as the experience of the treating doctor should be considered when making ARS recommendations. The paucity of clinical studies published by Align Technology regarding the effects of accelerated ARSs may indicate clinicians should proceed with caution. After all, it is the orthodontic provider who is liable for the results of treatment.⁷

Finally, the accuracy of CAT is a measure of how well the aligners achieve the tooth movements predicted by the virtual treatment plan. If the patient, or orthodontic provider is not satisfied with the result of treatment, he/she may decide to initiate a midcourse correction, refinement, or conversion to fixed appliances in order to obtain satisfactory results with treatment. Additional treatment following completion of the initial set of aligners increases OTT, which increases the burden of treatment and decreases profitability for the patients and provider, respectively.² Align Technology, Inc. claims 20% to 30% of patients treated with Invisalign might require either midcourse correction or additional treatment with refinement aligners, however, many orthodontists report 70% to 80% of their Invisalign patients require midcourse correction, case refinement, or conversion to fixed appliances in order to obtain a satisfactory result with treatment.⁸

Recent prospective clinical studies evaluating the efficacy of CAT using Invisalign have been conducted using the most current clinical protocols and aligner material. Grunheld et al⁹ evaluated post-treatment models of 30 patients who had non-extraction Invisalign treatment and determined Invisalign is capable of achieving predicted tooth positions with high accuracy, however, actual outcomes differ from the predicted outcomes. Their results further indicated the Invisalign system under-performs with tooth movements involving maxillary lateral incisors, canines, first premolars as well as posterior teeth in all dimensions. Interestingly, the upper and lower incisors tended to be more occlusal than anticipated, which would indicate the post-treatment overbite in patients with deep bites was larger than expected.

As a follow-up to an initial pilot study, Krieger et al¹⁰ reported moderate to severe levels of lower anterior crowding can be resolved via protrusion of the anterior teeth using Invisalign. Achieved tooth movements were accurately predicted by the post treatment ClinCheck[®] models

with the exception of overbite, which were on average 0.71mm from predicted values. These results agree with data from the prospective clinical trial completed by Kravitz et al¹¹, who determined extrusion (29.6%) and intrusion (41.3%) of anterior teeth is inaccurate. Thus, there seems to be a trend for a high degree of discrepancy between the planned and the achieved tooth movements in the vertical plane.

Some clinical studies and multiple case reports, however, have reported the Invisalign system is relatively successful in managing overbite correction. With outdated clinical protocols, Boyd and Vlaskalic¹² reported correction of deep bite is one of the most predictable movements possible with Invisalign. Additionally, Gioncotti et al¹³ concluded deep bites can be effectively treated while using Invisalign to level the dental arches via intrusion of anterior incisors. Finally, a well-designed retrospective study conducted by Khosravi et al¹⁴ used cephalometric analysis on a large sample size to determine CAT can effectively treat deep bites as well as open bites patients while avoiding negative changes in those with normal overbites.

However, the results of the studies supporting Invisalign as a means to correct deep, or open, bites should be interpreted with caution. When compared to fixed appliances, overbite correction with Invisalign in the Khosravi et al. study was only half as effective even after as much as three refinement treatments.^{14,15} Moreover, no studies have investigated the efficacy of overbite correction with accelerated Invisalign protocols, or in complex malocclusions such as: deep bites patients with spacing, or open bite patients with crowding.

A critical review of the published clinical studies and case reports investigating the accuracy of the CAT indicate the capabilities of Invisalign have improved, however, we still have much to learn regarding the biomechanics and accuracy of the Invisalign system. In order to become more proficient with Invisalign, orthodontic providers must gain more understanding of

the inaccuracies of the ClinCheck[®] software as well as limitations of CAT. Expanding the knowledge and experience of treating various types of malocclusions will enable clinicians to incorporate necessary over-compensations into their virtual treatment plans.

Increasing the rate of OTM by accelerating the complex cellular process of alveolar bone remodeling presents a potential way to improve the efficiency and efficacy of CAT. OrthoAccel Technologies, Inc. (Houston, TX) claims the application of low-frequency vibrations forces (30Hz) for 20 minutes per day using the AcceleDent Aura[®] device will result in a 50% increase in OTM and enable patients to utilize accelerated aligner schedules with improved efficacy.^{16,17}

Currently, there are very few clinical studies assessing the effect of vibration therapy on CAT. This is especially true for tooth movements in the vertical plane, which affect the patient's overbite. A recently conducted, well-designed randomized clinical trial found no evidence of the AcceleDent Aura device contributing to a patients ability to complete a series of aligner with a 1-week ARS.⁵ In addition to the completion rate, the study determined vibration therapy made no statistically significant difference in the reduction of lower incisor crowding.⁵ These findings do not support the 1-week ARS recommended by Align Technology, however, it is interesting to note the surprisingly high overall success rate (81%) reported in completing the series of aligners.

Therefore, it seems appropriate to decrease the ARS even further and investigate the efficacy of 4-day change regimens with and without vibration therapy in patients with mild-moderate malocclusions characterized by both spacing and crowding. The purpose of our study is to help clinicians further understand the effects of accelerated (4-day) Invisalign[®] and vibration therapy on overbite correction and classify which patients are good candidates for accelerated Invisalign therapy.

Specific Objectives and Hypotheses

The aim of this RCT is to determine the effect of vibration therapy and 4-day aligner schedule (DAS) on: (1) the accuracy of overbite correction.

The null hypotheses tested in this study were the following: (1) vibration therapy does not increase the accuracy of overbite correction and (2) 4-DASs do not increase the accuracy of overbite correction.

Material and Methods:

Trial design and any changes after trial commencement

This study was designed as a double blinded, single-centered 3-arm, parallel, prospective randomized clinical trial with 1:1:1 allocation ratio.

Participants, eligibility criteria and settings

Ethical approval was granted by the Office of Human Research Ethics at the University of North Carolina (reference number: 16-0167). The clinical trial was registered at the US National Institutes of Health (ClinicalTrials.gov) #NC NCT02868554. See CONSORT flow diagram (Figure 2).

The study population was drawn from patients pursuing Invisalign[®] treatment in the postgraduate orthodontic clinic of the University of North Carolina (UNC). Patients were included for participation based on the following criteria: (1) being within the ages of 18-65 years old, (2) good health determined by a current medical history, (3) full adult dentition including second molars in both dental arches, (4) normal pulp vitality and healthy periodontal tissues as determined by intraoral exam, (5) initial malocclusion with mild to moderate dental crowding or spacing ($\leq 6\text{mm}$), (6) non-extraction Invisalign treatment with ClinCheck treatment plans prescribing more than 21 active aligners with simultaneous tooth movement of anterior

teeth and no deviation from default amounts of tooth movements prescribed in each aligner stage, (7) no mid-course correction, or additional aligners, and (8) willingness to and ability to comply with study procedures, attend study visits, and complete the study protocol.

Patients were excluded from participation based on the following criteria: (1) individuals diagnosed with systemic diseases such as diabetes, hypertension, temporomandibular disorders, or cranio-facial syndromes, (2) chronic use of any non-steroidal anti-inflammatory medications, estrogen, calcitonin, or corticosteroids, (3) history of use or current use of bisphosphonate medication or other medication for treatment of osteoporosis, (4) current smoker (not within the last 6 months), (5) significant periodontal disease (>4mm pocket depth or >2mm recession), (5) active caries, or new dental restorations during treatment (6) initial malocclusions with severe crowding or spacing (>6mm), (7) impacted teeth and, or closure of extraction spaces, requiring fixed appliances or adjunctive procedures other than clear aligners, (8) ClinCheck treatment plans with less than 21 aligners, or plans that failed to start all tooth movement simultaneously, and finally, (9) failing to comply with research protocols.

Enrolled subjects were allocated into one of 3 groups: 14-DAS (control- G1), 4-DAS (G2), and 4-DAS plus vibration therapy using AcceleDent Aura[®] (G3). Informed consent and assent were obtained prior to initiating the clinical trial protocol. In total 67 patients were screened for eligibility, 34 patients were excluded for not meeting the previously mentioned criteria, and 33 patients were enrolled under the supervision of Dr. Bill Gierie, who is an Elite top 1% Invisalign provider and also serves as a KOL for Invisalign. Dr. Gierie was blinded to group allocation of all subjects during the initial set-up and approval of the ClinCheck treatment plan, however, he was made aware if the patient was in the study to ensure no additional modifications were requested to alter the rate of programmed tooth movement per aligner (0.25mm/aligner).

Once the aligners arrived from the manufacture, enrolled patients were scheduled for aligner delivery and randomly allocated to one of the 3 groups using third party randomization software.

According to group allocation and Invisalign[®] start date (To), customized aligner schedules were issued to all subjects and recall appointments were scheduled for data acquisition. Subjects in the control group (G1) were instructed to wear each aligner set 14 days. Subjects receiving an accelerated aligner schedule (G2/G3) were instructed to wear each aligner set 4 days. All subjects were instructed to wear each aligner at least 22 hours per day and progress to the subsequent aligner based upon their customized schedule. Subjects receiving vibration therapy (G3) were issued a fully charged Aceledent Aura[®] device with operating instructions and compliance counseling. Vibration therapy was applied for 20 minutes per day at a force of .25N (25g) at a frequency of 30Hz. G3 subjects were blinded from the fact that the Aceledent Aura device contains Fastrac[®] software which is a microprocessor that stores the date and duration of use each time the device was activated. All subjects were recalled at the following time points for data collection: T_{4-days}, T_{2-weeks}, T_{6-weeks}, and T_{12-weeks} after the Invisalign start date.

The investigator completed the following research steps at each recall visit: (1) obtain virtual models of maxillary and mandibular dental arches using Trios 3Shape scanner and (2) determine discomfort experienced by the subject at the onset of subsequent aligner delivery using the Faces Pain Scale[®]. Subjects were also asked to indicate the number of hours they typically wear the Invisalign trays and if analgesics were used to relieve discomfort associated with their treatment.

Under faculty supervision, orthodontic residents completed the following clinical steps specific to each recall visit: (To)[a] deliver aligner #1, (T_{4-days}) [a] deliver aligner #s: 2-4 to

G2/G3 subjects only, (T_{2-weeks}) [a] place composite attachments prescribed in the ClinCheck treatment plan and [b] deliver aligner #s: 2-3 to G1 subjects and aligner #s: 5-11 to G2/G3 subjects, (T_{6-weeks}) [a] deliver aligner #s: 4-6 to G1 subjects and aligner #s: 12-21 to G2/G3 subjects, (T_{12-weeks}) [a] terminate study protocol and continue treatment under the guidance of attending faculty, Dr. Bill Gierie.

Outcomes (primary and secondary) and any changes after the trial commencement

The primary outcome measure within the three groups was the percent accuracy of overbite (OB) correction following 12 weeks of treatment. OB was defined as the extent of vertical overlap, measured in mm, of the maxillary central incisors over the mandibular central incisors. For each subject at baseline (T₀) and following 12-weeks of treatment (T_{12-weeks}), the OB was determined on digital study models (.stl) captured with intra-oral scans. The percent accuracy of OB correction was determined by the following equation: the percent accuracy of OB correction 100% [(baseline OB – achieved OB)/(baseline OB – predicted OB)].

Because T_{12 weeks} in our study only reflected OB correction following the initial 12-weeks of treatment, the predicted OB for our subjects was determined as a percentage of the total predicted OB correction, which was determined by measuring the OB in the final digital models predicted by the ClinCheck software. For example, the equation for predicted OB in control group subjects (G1) was: [|initial OB| - (|initial OB - predicted OB| x |6 aligners/ total # of active aligners|)]. For subjects in the accelerated intervention groups (G2/G3), we used the same formula mentioned above but the percentage of achieved reduction in PCPDI was larger because the subjects completed 21 aligners rather than 6 aligners. Calculating the percent accuracy of OB correction helped to overcome the discrepancy between the amounts of OB correction predicted within each group. Positive percentages designated favorable OB changes (bite opening for deep

bites and closing for open bites), while negative percentages designated unfavorable changes in OB (bite deepening for deep bites and opening for open bites).

Prior to data analysis within each group, the subjects were stratified based on whether the predicted OB correction was simple, or complex. Subjects were determined to have simple OB correction if the pre-treatment malocclusion contained crowding and goal of treatment was to reduce the initial OB, or if the pre-treatment malocclusion contained spacing and the goal of treatment was to increase the initial OB. Conversely, subjects were determined to have complex OB correction if the pre-treatment malocclusion contained spacing and the goal of treatment was to decrease the initial OB, or if the pre-treatment malocclusion contained crowding and the goal of treatment was to increase the initial OB. (Figure 8)

Prior to obtaining T_0 , $T_{12 \text{ weeks}}$ and predicted OB measurements, we imported the stage final models (.stl) from the ClinCheck treatment plan as well as the scanned digital study models (.stl) from each time point into Geomagic DesignX64 software. For each digital model at each time point, a single blinded investigator (B.B) reproducibly superimposed the initial (T_0) and 12-week ($T_{12\text{-week}}$) maxillary models on stable reference points on the palatal rugae.¹⁸ Subsequently, initial maxillary ClinCheck models were superimposed to the T_0 maxillary models using a best-fit algorithm based on reference points selected on the occlusal surfaces of the teeth. Because these study models represented the same model at the same time point, the best-fit algorithm produced a very accurate superimposition verified by mesh deviations less than 0.01mm. Once the initial maxillary ClinCheck and T_0 models were superimposed, the final maxillary Clincheck model was superimposed using a transformation matrix corresponding to the newly superimposed initial Clincheck model. Finally, the mandibular study models for T_0 and $T_{12 \text{ weeks}}$ as well as the initial and final ClinCheck were oriented to their corresponding maxillary models

using a bite registration captured with the intra-oral scan. Superimposition of the maxillary study models was necessary to ensure the OB measurements were completed in the exact same viewpoint and the points used for OB measurement were projected in the same vertical axis. (Figure 9)

Once all digital study models were superimposed in the same x-, y-, z- axis coordinate system, the same blinded investigator (B.B.) selected points on the incisal edges of maxillary and mandibular central incisors determined to represent the greatest vertical overlap. OB measurements were completed with calibrated digital calipers (accurate to 0.01mm) within the Geomagic X64 software.

Daily compliance using the AcceleDent Aura[®] device as well as satisfying the use requirement of 20-22 hours per day for the Invisalign trays was monitored throughout the study. Compliance with the vibration device was measured using the OrthoAccel, Inc. proprietary software, FastTrac[®] and compliance with Invisalign was collected with a questionnaire during each recall appointment.

Sample size calculation

The main outcome measure in this study was the (1) percent accuracy of overbite (OB) correction during the initial 12-weeks of treatment. Sample size estimation was completed using G*Power 3.1 software and showed a total of 21 participants, 7 participants (7 OB measurements) in each treatment arm, was required to demonstrate a clinically significant difference in the primary outcome of a 75% increase in the accuracy of OB correction between G1 and G2/G3, with 80% power, a standard deviation of 0.1, and an alpha of 0.05, using two sample T-test, and with the null hypothesis of equal effect. In addition, to allow for a potential 30% dropout rate, the

sample size was increased to 30 subjects. A formal power analysis was not completed for the stratified OB data (simple vs complex) compared within each group.

Interim analyses and stopping of guidelines

No interim analysis was performed during the study. During the design of study protocol, we decided the trial would be stopped if any harm came as a result of the interventions.

Randomization

An independent, third party biostatistician, using an electronic program, R 3.4.2, completed randomization of the subject allocation sequence. All subjects enrolled within the study were randomized in blocks of 6 to the 3 groups that correspond to one of the 3 treatment options to be studied. Allocation concealment was secured by contacting the sequence generator for assignment. 10 subjects were randomized to the 14-DAS (G1), 12 subjects were randomized to the 4-DAS (G2), and 11 subjects were randomized to the 4-DAS plus vibration therapy (G3). All subjects enrolled within the study (33) received an allocation intervention.

Blinding

Blinding of either the patient, or the assigned orthodontic resident, was not possible during this clinical trial due to a lack of sham vibration devices. It was also the opinion of the investigator that a sham device was not a realistic way of eliminating the placebo effect, which has been repeatedly discussed in previous studies evaluating pain scores. However, the part-time faculty member (B.G.) was blinded during the initial set-up of the ClinCheck treatment plans and the research investigator (B.B.) was blinded during data analysis. The digital models used to perform the OB measurements were de-identified and assigned a three-digit code to ensure the investigator was unaware of the patient's intervention method.

Statistical Analysis

Descriptive statistics on demographic, clinical characteristics, and outcomes Invisalign treatment were calculated. Since a large correlation coefficient (0.25) was present between upper and lower teeth in the percent reduction of PCPDI, repeated measures ANOVA was used as the primary statistical method to account for the dependence. A categorical variable with 3 levels was created for the group in the linear mixed effects model with a random intercept. The statistical significance of the difference between groups in both primary and secondary outcomes was tested using a t-test obtained from the parameter estimation. Since there is no significant difference in baseline characteristics, we did not adjust for any covariates in the mixed effects model. P-values less than 0.05 were considered statistically significant. All of the statistical analyses were implemented using SAS 9.4 (Cary, NC).

Compliance data downloaded from the devices were analyzed. The difference the primary aim between compliers and non-compliers were measured using the Wilcoxon rank sum test. Self-reported aligner compliance data was gathered from the subject surveys and analyzed with a Wilcoxon rank sum test to measure the differences between the groups.

Results:

Participant Flow

Open enrollment began in May 2016 and continued until November 2017. 33 subjects (mean age, 32.3yrs; SD: 9.21; max: 57yrs; min: 18yrs) were randomized to one of 3 intervention groups: 14-day aligner schedule (G1), 4-day aligner schedule (G2), and 4-day aligner schedule + vibration therapy (G3). Data from 2 subjects were eliminated from the data sample prior to analysis because the ClinCheck[®] treatment plans did not initiate tooth movement simultaneously. In addition, 2 patients were eliminated following data analysis because the predicted OB

correction during the 12-week study period was less than the error of measurement (0.2mm). This resulted in the final analysis of 29 digital study models. The recruitment and follow-up of all subjects during the study is shown in the CONSORT flow diagram (Figure 2). No subject was lost to follow-up during this study.

Baseline Data

Table 3 shows the similarity in the distributions across treatment groups for demographic, predicted OB correction as well as the average number of aligners used per group. Table II displays the mean self-reported aligner use per day within each group. Table 4 and Table 5 indicate the differences in the desired simple and complex OB correction within each group, respectively. Figure 3 illustrates the compliance with the AcceleDent Aura[®] by subjects within G3.

Numbers analyzed for the primary aim (discrepancy between predicted OB correction and achieved OB correction)

Our results indicated the use of accelerated (4-day) aligners schedules with, our without, vibration tended to decrease the accuracy of OB correction. However, when analyzing the mean percent accuracy of OB correction (%) between all types of OB correction within each group, we did not find a statistically significant difference between G1 and G2/G3 ($P = 0.331, 0.064$) nor G2 and G3 ($P = 0.288$). Additionally, for simple and complex OB correction, mean percent accuracies of OB correction were not statistically different between the 3 groups ($P = 0.700, .915, 0.847$). (Figure 9) Surprisingly, when comparing the percent accuracies of OB correction of simple OB to complex OB correction within each group, there was a significant difference within each group ($P = 0.039, < 0.001, 0.046$) (Table 10).

Compliance was found to drop-off markedly during the period of the trial. Only 6 participants (54%) met the criterion of being considered as good compliers by using the vibration

device 75% of the time or more (Figure 3). The mean percent accuracy of simple OB correction in compliers was 48%, while in the non-compliers the mean percent accuracy was 53%. For complex OB correction, the discrepancy of OB correction was -8% for compliers and -10% for non-compliers, thus, showing vibration therapy had little effect on the accuracy of OB correction. The mean compliance with aligner use was within recommended range (20.9 hours per day) and the means of use within the groups was not statistically different (Table 3)

Error of the Method

To reduce effects of random measurement error and calculate intra-operator reliability, the same single operator (B.B) manually repeated the steps to measure the OB 3 times and allowed 1-weeks time to pass between measurements. For each model at each time point, the accepted OB value used to calculate the percent accuracy of OB correction was the average of 3 completed measurements. The Dahlberg¹⁹ measurement error calculations showed a 0.1mm difference between the initial and repeated measures.

Harms

There was no evidence of adverse events, or safety hazards, to the soft or hard tissues of the participants during the trial.

Discussion:

Main findings in the context of the existing evidence, interpretation

Undoubtedly, clear aligner therapy (CAT) has met the esthetic demands of the orthodontic patient and provider, but there continues to be a lack of clarity associated with treatment efficiency and the ability of clear aligners to achieve desired tooth movements. Previous clinical studies have attempted to help orthodontic providers understand the strengths and weaknesses of clear aligners as an orthodontic appliance, but the evidence is hardly

conclusive.^{10,11,20} It appears the efficacy of CAT is likely associated with the clinical characteristics of the pre-treatment malocclusion as well as the experience level of the orthodontic provider.¹¹

Orthodontic treatment time (OTT) using CAT is based on traditional biologic factors and clinical protocols, which are dictated by the manufacturer and orthodontic provider.

Additionally, treatment time with CAT is based on the need for refinement aligners if the initial series of aligners does not produce a satisfactory result. Supporters of the AcceleDent Aura[®] therapy claim micro-vibration therapy will increase the efficacy of CAT and allow accelerated aligner reactivation schedules (ARS), or number of days a patient wears each aligner set.²¹

However, a recently conducted RCT indicated vibration had no effect on the outcome of treatment when using 7-day aligner schedules.⁵ These results were very timely in that they give some evidence to support the 7-day ARS recently announced by Align Technology, Inc. for all Invisalign patients.⁶

In this RCT, we evaluated the effects of accelerated (4-day) CAT and vibration therapy on the accuracy of overbite correction. The demographics of our study sample were 64% female, however, this reflects a “real-world” scenario as females are generally more concerned with esthetics and duration of treatment.²² The average of age was similar between allocation groups (32.3yrs, SD: 9.85). To account for the significant difference in the predicted OB correction between the groups, we measured the percent accuracy of OB correction. Based on our data, accelerated (4-day) aligner schedules tend to exacerbate the accuracy of OB correction, however, we did not find a significant difference in the overall accuracy of OB correction between the groups. This finding likely resulted for the abnormally large standard deviations found within each group.

In an effort to explain why the standard deviations were so large in the analysis of overall OB correction, we stratified subjects into categories of simple and complex OB correction based on pre-treatment clinical characteristics (anterior spacing or crowding) and the desired effect of OB correction. The basis of our stratification was supported by well-established knowledge regarding the vertical side effects (relative intrusion or relative extrusion) associated with anterior space closure (lingual tipping) or anterior crowding (facial tipping), which might benefit, or negate, the desired OB correction. During anterior space closure with aligners, the crowns of the incisors tip lingually and retrocline, which causes relative extrusion and a bite deepening effect. With anterior crowding, the incisors expand facially and procline, which causes a relative intrusion and bite opening effect. Therefore, OB correction may be more accurate when the goal of treatment is to reduce OB with the presence of anterior dental crowding, or when the goal of treatment is to increase OB in the presence of anterior dental spacing (simple). Conversely, OB correction is less accurate when the goal of treatment is to reduce the OB in the presence of anterior spacing, or when the goal of treatment is to increase OB in the presence of anterior crowding (complex).

Our results indicated simple OB correction is significantly more accurate than complex OB correction within each group. For simple OB correction, the mean percent accuracy of OB correction was positive, meaning there was improvement in pre-treatment OB. However, for complex OB correction, the percent accuracy of OB correction was negative, indicating the pre-treatment OB worsened. Surprisingly, we did not find a significant difference in simple or complex OB correction between each group. This finding may indicate the most important factor in determining the accuracy of OB correction with aligners has less to do with the aligner schedule or vibration than the type of OB correction.

The existing literature reports mixed results regarding the accuracy of OB correction with aligners, however, our study is the first to specifically investigate the accuracy of OB correction with specific pre-treatment characteristics. Our data suggests simple OB correction is relatively successful with an accelerated (4-day) aligner schedule without vibration. These findings agree with the results of published by multiple clinical studies^{14,15}. Conversely, our data suggests complex OB correction is relatively unsuccessful when using CAT and the result of treatment is exacerbated when using an accelerated (4-day) aligner schedule with, or without, vibration therapy. These findings may provide merit to the conclusions published Krieger et al²³ and Kravitz et al⁸ regarding the inability to resolve deep bites when using CAT.

Our study suggests OB correction may be a weakness of CAT, however, simple OB correction is more accurate than complex OB correction. Additionally, our study suggests accelerated (4-day) aligner schedules are not recommended when the type of OB correction desired is complex. The significantly reduced accuracy of complex OB correction within each group indicates significant compensations are indicated to obtain clinically acceptable results. In regards to treatment efficiency of complex OB correction, accelerated (4-day) aligner regimens may not reduce OTT because the increased need for compensations will increase the number of aligners in the series relative to a 2-week ARS. Finally, vibration therapy does not play a significant role in the efficacy of OB correction with CAT, thus, the additional fee associated with the adjunctive therapy is considered unjustified.

No other studies have evaluated specific pretreatment clinical characteristics (such as anterior spacing, or crowding) with respect to accuracy of OB correction with CAT. More long-term clinical studies evaluating the performance of accelerated aligner schedules are necessary. A study investigating the effect of 4-DAS and 7-DAS on the accuracy of simple and complex

OB correction seems appropriate. It would also be beneficial to gather information regarding the performance various aligner schedules with respect to specific types of tooth movements. With that data, provider can make a more informed decision with regard to aligner schedule based on pre-treatment findings instead of relying on Align's recommendation, which may not be best for all patients.

Limitations

Clinical studies that provide good-quality patient care while testing alternative treatments must, by their nature, involve compromises. One limitation of our study was not blinding the research subjects to their intervention group. However, significant patient blinding was impossible while maintaining the clinical applicability of the study. Previous studies have used sham vibration devices, but with questionable efficacy in regards to blinding. The results of our study were also subject to the potential for poor patient compliance with the Invisalign, or vibration device. Although the recall surveys encouraged subjects to wear their aligners for 20-22 hours per day, we were unable to verify the daily frequency of aligner use for each patient. In addition to the effects of compliance with the vibration devices and the Invisalign trays, our results were limited by a small sample size once the subjects were stratified into groups of simple and complex OB correction. We also did not account for the effect of posterior teeth in the OB measurement but according to Roozbeh et al¹⁴, most OB changes with CAT result from maxillary and mandibular incisor movement. Finally, we do not know the short versus long-term effects of vibration therapy on OTM, but the short (12-week) evaluation period in this trial may not have allowed for the cumulative affect of vibration therapy.

Generalizability

The demographics and clinical characteristics associated with our research subjects are representative of the adult population currently seeking orthodontic treatment and are concerned with the issues of esthetics and duration of treatment. The results and conclusions made from our study have generalizability only to the accuracy of OB correction when using accelerated (4-day) Invisalign. The challenges we experienced related to patient compliance wearing the aligners and using the vibration device reflect real-world issues common throughout all orthodontic treatment outside of a research setting.

Conclusions:

1. Pre-treatment characteristics can be used to classify the desired OB correction using clear aligners
 - a. Simple OB correction occurs when the goal of treatment is to reduce OB with the presence of anterior dental crowding, or when the goal of treatment is to increase OB in the presence of anterior dental spacing.
 - b. Complex OB correction occurs when the goal of treatment is to reduce the OB in the presence of anterior dental spacing, or when the goal of treatment is to increase OB in the presence of anterior dental crowding.
2. Accelerated (4-day) aligner schedules are not recommended for complex OB correction
3. Vibration had no effect on the accuracy of OB correction
4. OTT for patients utilizing a accelerated (4-day) aligner schedules with, or without vibration, may not be reduced due to an increased potential for mid-course correction and/or refinement
 - a. All OB correction needs to be overcorrected in ClinCheck

- i. Complex deep bite: extensive overcorrection
 - 1. 4-day aligner schedules may create side effects equivalent to closing space on a superelastic arch wire
- b. Complex open bite: stage extrusion after crowding is resolved, use IPR and simultaneous retraction

Table 3: Sample Demographics and Predicted OB Correction

		Group 1		Group 2		Group 3		Total		P- value
Sex		n	%	n	%	n	%	n	%	G1 vs G2, G1 vs G3, G2 vs G3
	Male	5	50	3	25	4	36	9	36	
	Female	5	50	9	75	7	64	19	64	
Age (y) (mean \pm SD)		35.5 \pm 10.45		31.25 \pm 9.25		30.33 \pm 7.95		32.36 \pm 9.21		0.54
Overall Predicted OB correction (mm)		1.01 \pm 0.18		1.37 \pm 0.61		0.95 \pm .60		1.11 \pm 2.30		<0.001, 0.07, 0.08
Number of aligners (mean)		30.55		32.3		32.6		31.8		0.23, 0.15

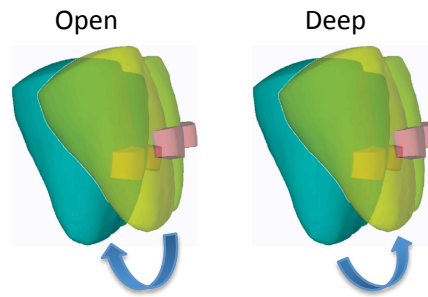
Table 4: Predicted Simple OB change by treatment group in 12 weeks

Mean desired OB Change in 12 weeks (mm)	N	Mean change (mm)	SD	G1	G2	G3
Simple				P-value		
G1	4	0.521	0.154	X		
G2	6	1.374	0.832	0.074	X	
G3	2	1.807	0.560	0.049	0.438	X
Total	12	1.160	0.774			

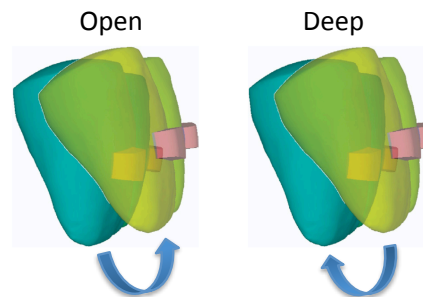
Table 5: Predicted Complex OB change by treatment group

Mean desired OB Change in 12 weeks (mm)				p-value		
Complex	N	Mean change (mm)	SD	G1	G2	G3
G1	4	0.433	0.208	X		
G2	6	1.364	0.336	<.001	X	
G3	7	0.709	0.332	0.178	0.002	X
	17	0.875	0.435			

Figure 8: Simple and Complex Overbite (OB) Correction



Simple: relative extrusion favors desired bite deepening and relative intrusion favors desired bite opening



Complex: relative extrusion negates desired bite opening and relative intrusion negates desired bite deepening

Figure 9: Superimposition of maxillary models and Overbite (OB) measurement

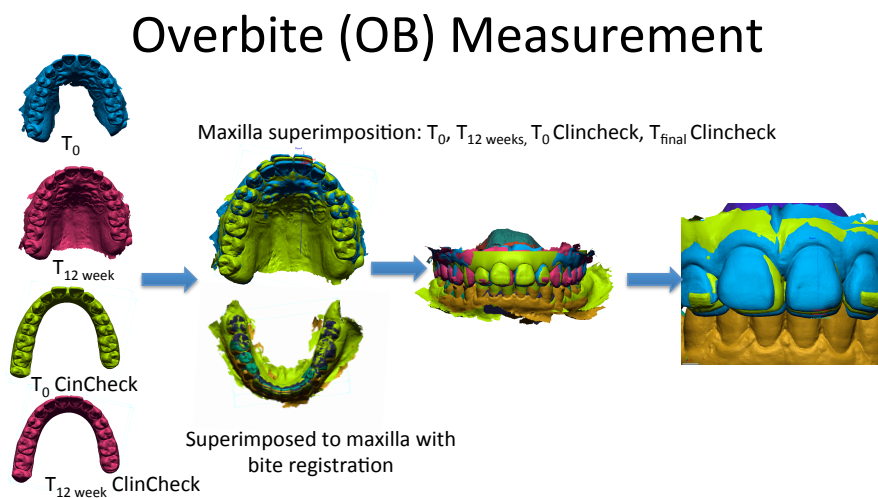


Figure 10: Overall Accuracy of Overbite (OB) Correction in 12 weeks (%)

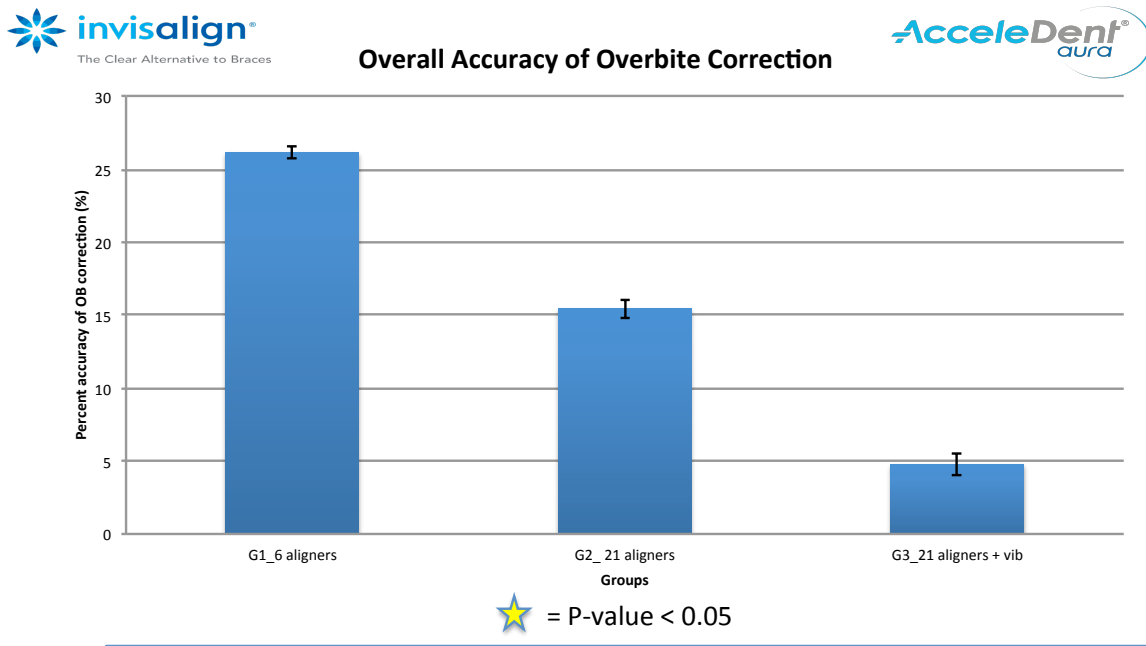
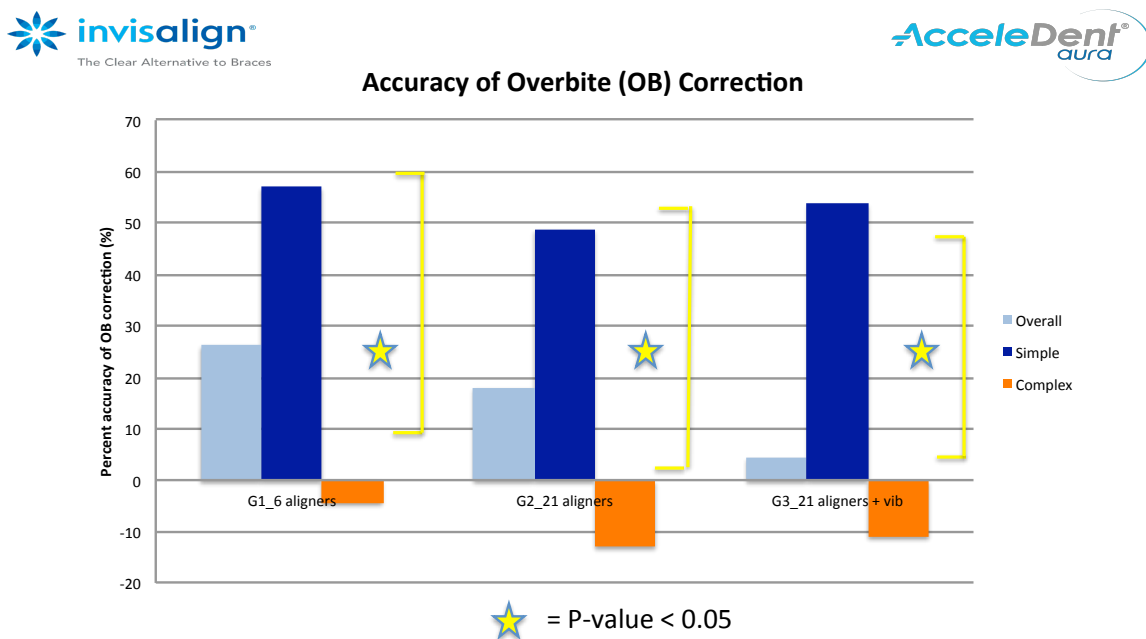


Figure 11: Accuracy of Simple vs Complex Overbite Correction in 12 weeks (%)



REFERENCES

1. Hershfield J. Edward H. Angle and the malocclusion of the teeth. *Bull Hist Dentl.* 1979;27(2):79-84.
2. Uribe F, Padala S, Allareddy V, Nanda R. Patients', parents', and orthodontists' perceptions of the need for and costs of additional procedures to reduce treatment time. *Am J Orthod Dentofac Orthop.* 2014;145(4 SUPPL.):S65-S73. doi:10.1016/j.ajodo.2013.12.015
3. Walton DK, Fields HW, Johnston WM, Rosenstiel SF, Firestone AR, Christensen JC. Orthodontic appliance preferences of children and adolescents. *Am J Orthod Dentofac Orthop.* 2010;138(6):698.e1-698.e12. doi:10.1016/J.AJODO.2010.06.012
4. Fink DF, Smith RJ. The duration of orthodontic treatment. *Am J Orthod Dentofac Orthop.* 1992;102(1):45-51. doi:10.1016/0889-5406(92)70013-Z
5. Katchooi, Mina; Cohanin, Bobby et. al. Effect of supplemental vibration on orthodontic treatment with aligners: A randomized trial. *Am J Orthod Dentofac Orthop.* 2018;153:336-346.
6. Technology A. ALIGN TECHNOLOGY INTRODUCES ONE-WEEK ALIGNER WEAR FOR INVISALIGN(R) TEEN AND FULL PRODUCTS.
7. Laurance J. Accelerated orthodontics or accelerated liability? *Am J Orthod Dentofac Orthop.* 2014;145(4):148-151.
8. Kravitz ND, Kusnoto B, BeGole E, Obrez A, Agran B. How well does Invisalign work? A prospective clinical study evaluating the efficacy of tooth movement with Invisalign. *Am J Orthod Dentofac Orthop.* 2009;135(1):27-35. doi:10.1016/j.ajodo.2007.05.018
9. Grünheid T, Loh C, Larson BE. How accurate is Invisalign in nonextraction cases? Are predicted tooth positions achieved? *Angle Orthod.* 2017;87(6):809-815. doi:10.2319/022717-147.1
10. Krieger E, Seiferth J, Saric I, Jung BA, Wehrbein H. Accuracy of invisalign® treatments in the anterior tooth region. *J Orofac Orthop / Fortschritte der Kieferorthopädie.* 2011;72(2):141-149. doi:10.1007/s00056-011-0017-4
11. Kravitz ND, Kusnoto B, BeGole E, Obrez A, Agran B. How well does Invisalign work? A prospective clinical study evaluating the efficacy of tooth movement with Invisalign. *Am J Orthod Dentofac Orthop.* 2009;135(1):27-35. doi:10.1016/j.ajodo.2007.05.018
12. Boyd RL, Vlaskalic V. Three-Dimensional Diagnosis and Orthodontic Treatment of Complex Malocclusions With the Invisalign Appliance. *Semin Orthod.* 2001;7(4).

13. Giancotti A, Mampieri G, Greco M. Correction of deep bite in adults using the Invisalign system. *J Clin Orthod*. 2008;42(12):719-26; quiz 728.
<http://www.ncbi.nlm.nih.gov/pubmed/19276568>.
14. Khosravi R, Cohanin B, Hujoel P, et al. Management of overbite with the Invisalign appliance. *Am J Orthod Dentofac Orthop*. 2017;151(4):691-699.e2.
doi:10.1016/J.AJODO.2016.09.022
15. Huang GJ. Stability of deep-bite correction: A systematic review. *J World Fed Orthod*. 2012;Volume: 1(s).
16. Pavlin D, Anthony R, Raj V, Gakunga PT. Cyclic loading (vibration) accelerates tooth movement in orthodontic patients: A double-blind, randomized controlled trial. *Semin Orthod*. 2016;21(3):187-194. doi:10.1053/j.sodo.2015.06.005
17. Acceledent.com.
18. Choi DS, Jeong YM, Jang I, Jost-Brinkmann PG, Cha BK. Accuracy and reliability of palatal superimposition of three-dimensional digital models. *Angle Orthod*. 2010;80(4):497-503. doi:10.2319/101309-569.1
19. Dahlberg G. Statistical methods for medical and biological students. *New York Intersci Publ*. 1940.
20. Buschang PH, Ross M, Shaw SG, Crosby D CP. Predicted and actual end-of-treatment occlusion produced with aligner therapy. *Angle Orthod*. 2015;85(5):723-727.
21. Bowman SJ. The effect of vibration on the rate of leveling and alignment. *J Clin Orthod*. 2014;48(11):678-688.
22. Walton DK, Fields HW, Johnston WM, Rosenstiel SF, Firestone AR, Christensen JC. Orthodontic appliance preferences of children and adolescents. *Am J Orthod Dentofac Orthop*. 2010;138(6). doi:10.1016/j.ajodo.2010.06.012
23. Krieger E, Seiferth J, Marinello I, et al. Invisalign® treatment in the anterior region. *J Orofac Orthop / Fortschritte der Kieferorthopädie*. 2012;73(5):365-376.
doi:10.1007/s00056-012-0097-9