EFFECT OF REDUCING THE INCREMENTAL DISTANCE OF TOOTH MOVEMENT PER ALIGNER WHILE MAINTAINING OVERALL RATE OF MOVEMENT ON SELF-REPORTED DISCOMFORT IN INVISALIGN PATIENTS.

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An Abstract Presented to the Graduate Faculty of
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Abstract

Purpose: To compare the effects of reducing the incremental distance per aligner while maintaining the velocity of tooth movement on self-reported discomfort in patients being treated with Invisalign (Align Technology, Santa Clara, California). **Materials and Methods:** A prospective, longitudinal study of patients selected in private practice for treatment with Invisalign who completed questionnaires prior to treatment, and after placement of aligners at 6 hours, 24 hours, 2, 3, 7, 8, 9, 14, 15, and 16 days. Approximately half the patients followed the default schedule suggested by Align, wearing each aligner for 14 days. The other group received aligners prescribed to move the teeth half the default distance, but changed their aligners after only 1 week. The total distance the teeth were forced to move in both groups were the same. The level of discomfort was measured using a Visual Analog Scale (VAS). **Results:** 38 patients completed the surveys. No significant differences were found after insertion of the first aligner in median pain scores. At 8 days after insertion, patients in the experimental group reported significantly more discomfort than the traditional group, as they had changed to their second aligner while the traditional group reported almost no pain remaining on their first aligner. At 14 days following insertion, when the traditional group changed aligners, they experienced significantly more pain than the experimental group who did not change aligners. No significant differences were found in the amount of pain reported by patients when comparing the dates on which they respectively changed aligners. **Conclusions:** Patients following Align's traditional protocol in which teeth are forced to move .25mm every 2 weeks do not experience more pain than patients whose trays force teeth to move half that distance and change twice as often.

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DEDICATION

This paper is dedicated to my parents, whose tireless support has allowed me progress this far.

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Chapter 1: Introduction

Pain can only be defined in contrast to pleasure. It is an experience so basic to the human condition, so universal and ubiquitous that attempting to define the experience itself is unnecessary. Its purpose however bears discussion. Pain causes withdrawal from situations. The nervous system that detects and registers perception of these unpleasant sensations serves to protect individuals from physical harm or the potential thereof. At its core, pain is protective. A hot shower is pleasurable and refreshing to a point, but increasing the temperature increases discomfort, likely to a point where an individual would take an action to prevent tissue damage. In this case, the discomfort disappears upon removal of what is known as a noxious stimulus. Suffice it to say that pain is useful from an evolutionary perspective. Pain can also signal damage that has already occurred. If the temperature of the shower rises too quickly for an individual to respond prior to injury, then perception of pain from the burn continues long after the hot water is absent.

Primary in the perception of pain is the nervous system, both peripheral and central. The peripheral nervous system detects and transmits, while the central nervous systems modulates and perceives. In the case of burns, the body reacts by initiating various types of signaling mechanisms that communicate messages to the cells of the body that damage exists that requires repair. The organism's reaction to tissue damage is known as inflammation. Whether damage is the result of a bacterial infection, trauma from a stab wound, spending too much time on the beach without sunscreen, being bitten by a snake, or even the conscious choice to undergo orthodontic treatment, the body will react with inflammation, which acts both to protect the area and to initiate healing though

signaling that initiates appropriates processes. In addition to the nervous system's ability to detect potential damage (nociception), as in the example of increasing shower temperature, the system's detection and perception system for pain is tightly intertwined with the process of inflammation. The protective action of inflammation acts through the pain system. An individual with a broken ankle is unlikely to cause further damage partially because of a pain response on heightened alert, known as hyperalgesia. Inflammation's reparative action is through chemical mediators that: 1) initiate a variety of mechanisms leading to damaged tissue removal and repair and 2) lower the threshold for pain signals to be carried through the nervous system. The repair and the unpleasant experience are to some degree the same process. The critical point is that there is a duality of function to the inflammatory response.

When orthodontic treatment changes a tooth's position within bone, two simultaneous processes of bone resorption and apposition are at work. Mediated by cells of the periodontal ligament and vasculature, the bone surrounding the tooth changes while the tooth and its attachment apparatus remain intact. When orthodontic textbooks discuss the role of force and pressure in the process of these changes, they refer to two variations of osteoclast mediated bone resorption called frontal and undermining resorption. Reitan first suggested that "light forces" cause partial occlusion of blood vessels within the PDL.[1] This precedes local cellular differentiation and resorption of bone immediately adjacent the PDL. In contrast, "heavy forces" are thought to completely block circulation, which leads to sterile ischemic necrosis of nearby tissue. Historically it has been taught and is still taught that the amount of heavy force, and thus, "undermining" resorption is responsible for greater discomfort experienced by the

patient.[2,3] As no local blood supply is available, osteoclasts are recruited from adjacent marrow and vasculature to remove bone at a relative distance from the PDL resulting in a more stepwise movement of teeth. Roberts studied cellular kinetics and showed that osteoclasts arrive at temporally spaced points.[4] Proffit refers to these as "waves", with the first time point representing differentiation of local cellular population and the second infiltration of osteoclasts from more remote areas of the vasculature.[2] Around 48 hours, the first osteoclasts derived from the local progenitors within the PDL appear, and later a second group arrives from what is though to be hematogenous origin. Experimental data linking pain to force is controversial. Clarification of this relationship would help orthodontists understand and control one of the most negative side effects of treatment.[5]

Studies in the medical literature of pain have linked the subjective experience of pain to inflammation and ischemia via various mediators and cellular signaling molecules. Orthodontic research specifically has shown many of these same mediators are present in the periodontium subsequent to force application and during tooth movement. When heavier forces are applied to teeth and the periodontal ligament, it has been shown in dogs that larger areas of ischemic necrosis occur.[6] Although it is widely taught in orthodontics that lighter forces translate into a more comfortable experience for the patient, the literature does not support a strong relationship. The current study design draws on previous experiments that attempted to compare the patient's self-reported discomfort between different types of treatments. In previous studies, investigators have tried to determine whether various brackets or separators cause the patient relatively more or less discomfort. They have also compared various wire materials and diameters that would presumably deliver different force levels to the teeth in the initial stages of

treatment, and studied which patients were more affected. The present study investigated a treatment modality that has not been studied relative to force levels, thermoplastic aligners manufactured by Align Technology, called Invisalign.

Thermoplastic aligners work by forcing teeth to move in small stages or increments. Each new aligner is a setup of the next desired position of the teeth and it applies force to the crowns of the teeth until the teeth occupy this new position. This is possible because the increments are small and because the trays are somewhat elastic. We presume that the force level delivered to the teeth is a function of the modulus of elasticity of the tray as well as the amount that the tray can be said not to "fit". The present study attempted to evaluate the effect of reducing by half the incremental distance of tooth movement per tray, which would reduce the amount of force delivered to the teeth. Because we did not wish to alter the overall rate of tooth movement or affect the duration of treatment, the experimental group received twice the number of aligners normally prescribed by Align and changed them weekly as opposed to the typical change that occurs every two weeks. Patients rated their discomfort at rest and while chewing using a VAS and also answered yes/no questions related to compliance and use of analgesics. Patients reported at ten time points over the first 16 days of treatment. The selection of these time points was based on results from similar studies that investigated other treatment modalities.

Chapter 2 – Review of the Literature

Significance of Pain in Orthodontic Treatment

One of the most important factors deterring people from seeking orthodontic treatment is the fear of pain.[5] Approximately 90% of patients report that they experience pain during orthodontic treatment and around one third of patients think about ending treatment before it is complete due to the magnitude of the pain.[12] Scheurer et al. reported the mean intensity of pain on a 100 mm Visual Analog Scale (VAS) was 42 at 24 hours.[7] They also reported that 18% of his patients reported sleep disturbances, defined as being awakened in the night from the pain of orthodontic appliances. Jones and Chan showed 22% of patients reported sleep disturbances.[8] According to Brown and Moernhout, some patients are unable to sleep through the night and are forced to consume pain relieving medications to cope with the distress of orthodontic treatment.[9] All orthodontic procedures produce some pain, including separator placement, arch wire placement and activations, applications of orthopaedic forces and debonding. [8,10,11] Types of pain reported by orthodontic patients include pressure, tension, ache, and tooth soreness.[12] 58.5% of patients report agreed or agreed strongly with the statement, "I have pain for a few days after an appointment" and 21.9% reported that pain due to treatment influenced a dietary change.[13] Jones reported in a survey using numerical pain scaling that a significant proportion of patients reported experiencing severe or moderate discomfort.[14] Jones and Chan showed that the level and duration of pain experienced by patients on placement of an initial arch wire were greater than the pain from premolar

extractions.[8] Pain is a major factor in missed appointments and is a primary reason for noncompliance, including oral hygiene.[15] Tayer et al., surveying adults, found pain to be the most discouraging part of orthodontic treatment.[16] In one study, 8% of patients discontinued treatment due to pain.[17]

Previous studies have undertaken to investigate if there are differences in techniques to manage treatment variables. Pain is complex, multivariate, subjective and widely variable among individuals. Many have tried to determine whether varying mechanics, treatment modality, patient psychology and anxiety levels, analgesic medication, and force levels could have an effect on the intensity or duration of pain reported by the patient.

Pain

One of the most critical functions of the nervous system is to alert the organism to the possibility or reality of tissue damage. An organism's ability to avoid damage has an obvious role in its survival. The systems involved in communicating the source, nature, and intensity of the threat are extremely complex, involving multitudes of cells, chemicals, second messenger cascades, electrochemical nerve potentials, and central nervous system modulation. Adding further complexity are the interactions with psychological phenomena such as fear, anxiety, and stress. The body recognizes pain first through nociception, defined as the neural processes of encoding and processing noxious stimuli.[18]

The nociceptor is a nerve cell with the ability to detect potential or actual damage and translate the signal into electrical energy. In quantifying and defining aspects of pain for the purposes of scientific study, the terms pain threshold and pain tolerance are often used. Threshold is the slightest pain detected by the individual while tolerance is highest level of pain the individual is willing to tolerate.[19] The process of pain perception does not operate as a simple relay system, with a certain magnitude of input resulting in a predictable level of perceived pain response. Instead, the system can be modified, as mediators modify neurons to produce hyperalgesia, where a slightly painful stimulus may result in an unexpectedly high level of pain. Allodynia describes the condition where a lowering of the pain threshold results in a stimulus not typically capable of causing pain eliciting a painful sensation. A sponge bath, for example, is excruciating for a burn victim. Numerous receptor types exist to communicate various types of information to the organisms central processing apparatus, including C-fibre mechano-heat receptors which can communicate a burning sensation, as well as A-fibre nociceptors that are thought to provoke pricking, sharpness and possibly aching pain.[20] Bergius et al. state it is important for the clinician to be aware that pain is not a simple conduction of noxious impulses via several synapses to the cerebral cortex, where it is sensed and acted upon.[19]

In order to explain the lack of predictability and confusion related to the actual pain experiences of patients, Melzack et al. offered the Gate Control Theory to describe how the peripheral signals are modulated at different locations. Throughout most of the body, signals are received in the dorsal horn of the spinal cord. The spinal cells receive additional input from other neurons that serve to either open or close the gate allowing the signal to proceed to the brain.[21] In the face and jaws, pain information carried by the

trigeminal nerve synapse directly into the brain stem pons in the trigeminal spinal nucleus, which functionally is analogous to the spinal cord dorsal horn.[22]

Variables Affecting Pain

It is of consequence when studying pain in groups of people to control for characteristics that may influence their tendency to report pain, such as sex, age, and psychological well-being. A comprehensive systematic literature review conducted by Racine et al. in 2012 evaluated the past ten years of research on sex/gender differences.[23,24] At present it may be considered the definitive document on the subject, as it examined 172 articles. They concluded that females and males have comparable thresholds for cold and ischemic pain, while pressure pain thresholds are lower in females than males. There is strong evidence that females tolerate less thermal and pressure pain than males, but this is not the case with ischemic pain. In the medical literature that has examined pain, cold pain was typically induced by immersing a body part in cold water. Ischemic pain was induced with a tourniquet. The majority of the studies that measured pain intensity showed no sex difference in many pain modalities.[23] The aforementioned review was the first of two parts, and evaluated studies that experimentally induced pain in healthy individuals. The second part of the review examined biopsychosocial factors and concluded that women are more likely than men to report a variety of recurrent pains, in multiple body areas, which are more often described as being more severe and frequent compared to men.[24] None of twelve studies that examined a woman's stage in the menstrual cycle detected an effect.[24]

Jones and Chan found no significant difference with respect to pain between the sexes.[8] Erdinc and Dincer found no gender differences regarding the tolerance of pain.[25] Ingersoll states that while men are willing to tolerate more pain than women, there is not a difference in what men and women report as their pain threshold.[26] Bergius cites the cultural normative belief that men can "take more pain" and concluded that sex differences in pain behavior may reflect the influence of culture rather than differences in physiology.[19] A study by Fernandes and coworkers confirmed these results.[27] However, Scheurer et al. did find significant differences in reported mean pain intensity in a sample of 93 females and 77 male patients.[7] They speculated that part of the disagreement with other studies may be cultural because their sample was drawn from a German-speaking area of Switzerland. Miller et al. did not find differences in sex when comparing fixed therapy to Invisalign during a seven day study self reported pain using the VAS.[28] Nalbantgil et al. found no sex differences when studying the pain of tooth separation using a VAS.[29]

Anxiety has been cite as a pain contributor, and Bartlett et al. found that a phone call from a health-care provider reduced self-reported pain and anxiety.[30] Sergl and associates found that the psychological well-being of the individual affects pain perception.[31] Bergius et al. eached similar conclusions.[19] Both concluded that force levels were less important.

Age has sometimes been considered to be a factor in the reporting of pain. Several studies showed that adults perceive more pain than adolescents.[8,32] Fernandes et al. showed that adults perceive more pain than adolescents.[27] Jones and Chan reported that patients older than 16 reported significantly more pain than those fifteen years of age or

under.[8] However Ngan et al. found no significant differences between older and younger age groups.[12]

In sum, the evidence is contradictory as to whether one group or another experiences or reports more discomfort. It seems upon review of the orthodontic literature that variables like age, gender, and psychological state fail to reliably predict the magnitude of pain perception, though there is wide variation among individuals. For example, while it may be possible to conclude that one person will report more pain under stressful conditions than they would when calm, it is incorrect to conclude that individual would report more pain than another individual who reported feeling calm, because the second individual's baseline tolerances and thresholds were likely not initially equivalent.

Measurement of Pain

The measurement of pain experience is necessarily subjective and relies on self-reports. Among the techniques to measure pain in patients, the VAS is established as the most accurate and reliable. It is the most commonly used numeric scale at present.[19] It is more sensitive than the verbal descriptor scale when considering successive responses to treatment.[33] There is high correlation between successive measurements of pain severity.[34] Even young children are able to understand it.[25] Otasavic et al. states that although the objective evaluation of pain is difficult and can be altered by psychological, sociocultural, and environmental factors, the VAS is the most reliable method of measuring pain perception.[13] Ngan et al. has stated that the method is reproducible, it

eliminates interpretive differences in verbiage of other methods, and that it is able to report changes that are superior to verbal descriptive scales.[12] When considering reproducibility and ease of measurement, the VAS has been found superior to other pain scales.[35]

Inflammatory Chemical Mediators Directly Affect Pain

According to Levine and Reichling, inflammation is the single greatest cause of pain; pain involves various mechanisms by which chemicals sensitize and increase the activity of neurons responsible for communicating pain signals.[36] The inflammation can isolate the site of injury and protect the organism from further damage, and the process is also responsible for the removal of damaged tissue and the orchestration of local repair.[36] In most cases, loss of function is because patients experience hyperalgesia and allodynia. It is well established that many inflammatory mediators are directly responsible for hyperalgesia, including prostaglandins, leukotrienes, serotonin, adenosine, histamine, interleukin 1, interleukin 8, and nerve growth factor.[36] Kawabuta found that among the prostanoids (prostaglandins, leokotrienes, hydroxyacids), prostaglandin E2 and perhaps PGI2 (prostacyclin) have the greatest impact on processing of pain signals.[37] In the British Journal of Anaesthesia, Dray described prostaglandins as sensitizing sensory neurons, reducing their activation threshold and enhancing their responses to other stimuli.[38] Further, he noted the cytokines IL-1beta, IL-6, IL-8, and TNF alpha are capable of producing powerful hyperalgesia, and credits the neurotrophin NGF as being capable of the same.[38] Hyperalgesia may be induced in nociceptors due to their

sensitization by inflammatory mediators, including bradykinin, histamine, serotonin, and prostaglandin E.[20] One of the ways the nervous system detects injury to tissue is through the release of various mediators that are responsible for much of the inflammatory process. Although the following list is not comprehensive, Levine cites bradykinin, prostaglandins, leukotrienes, serotonin, histamine, substance P, thromboxanes, platelet activating factor, protons, and free radicals as contributors to inflammation and pain. Also produced when damage occurs are cytokines like interleukins, tumor necrosis factor and nerve growth factor, a neurotrophin.[36] These mediators have various roles: directly stimulating pain receptors, activating inflammatory cells that later release other pain causing substances, lowering action potential thresholds, and contributing to the state of hyperalgesia.[20] It is important to remember that while the mechanisms for signal transmission may be complex, elevated concentrations of the above molecules typically means that pain and inflammation are localized in the referenced tissue.

Orthodontic Treatment Causes Inflammation and Ischemic Necrosis

Although many different types of noxious stimuli exist, in orthodontics it is most appropriate to discuss pain related to inflammation and ischemia. The presence and roles of pain-inducing inflammatory mediators were first described in the medical literature. Numerous orthodontic studies have confirmed their presence in the PDL during the process of orthodontic tooth movement.

According to Krishnan, the perception of orthodontic pain is part of an inflammatory reaction caused by changes in blood flow following orthodontic force

application.[39] Orthodontic treatment is based on the principle that if prolonged pressure is applied to a tooth, tooth movement will occur as the bone around the tooth remodels.[2] The bony response of resorption and apposition that occur selectively at different locations is controlled by the periodontal ligament, which serves as the attachment to the tooth, and occupies a space of about one half millimeter around the entirety of the root. The periodontal ligament consists mainly of bundles of collagenous fibers that insert into both the cementum of the tooth and the dense plate of bone surrounding the PDL that can be observed radiographically as the lamina dura. In addition to the fibers, there are cells and fluid. The cellular population consists mainly of undifferentiated mesenchymal cells, which can form both fibroblasts and osteoblasts that regulate the collagen and bone respectively. During the removal of tissue, osteoclasts and cementoclasts are present; these are multinucleated giant cells derived from the blood. Though not present in great number, there are also blood vessels and nerve endings in the PDL. The free nerve endings act as nociceptors while other receptors, called proprioceptors, communicate information regarding tooth position in space.

The classic concept of tooth movement is known as the pressure-tension theory; it attributes the movement of teeth to cellular differentiation and activity due to chemical messengers that appear as a result of an alteration in blood flow within the PDL. This alteration in blood flow is due to the fact that when enough pressure is applied and the tooth is displaced within the socket, the ligament is compressed in some areas and stretched in others. Within a few minutes, a change in the local chemical environment occurs within the PDL fluid, manifested as relative changes in concentrations of oxygen and other metabolites. It is thought that these changes lead to differentiation and

activation of the cells responsible for bone remodeling. Grieve showed elevated levels of IL-1beta and Prostaglandin E2 when drawing fluid from the gingival crevicular fluid in human patients during orthodontic tooth movement.[40] Bergius et al. stated that pain is not reported for at least two hours after activation of appliances, that pain typically lasts for three days following its onset, and that it is still unclear why pain arises during orthodontic tooth movement.[19]

According to Yamaguchi et al., orthodontic forces are known to produce mechanical damage and inflammatory reactions in the periodontium.[41] Using low energy laser irradiation, levels of these two inflammatory mediators IL-1 beta and Prostaglandin E2 were reduced, as was pain.[41] Uematsu et al. found orthodontic force results in the presence of prostaglandins, Interleukin-1, IL-6, and tumor necrosis factor alpha in the PDL.[42] Cytokines and nitric oxide have been shown to be present, which are to be known inflammatory mediators and cellular signalers.[43] Davidovitch and Shamfield showed in animals that levels of cAMP, a known chemical messenger with a role in cellular differentiation, increased within four hours of sustained pressure.[44] Further, both Prostaglandin E and Interleukin-1 beta levels increase shortly after an increase in pressure.[5] Prostaglandin E is important for its unique ability to stimulate both osteoblasts and osteoclasts.[2] It is also the best known lipid mediator that contributes to the processing of pain.[37] The changes in blood flow that result from orthodontic force application results in rising levels of inflammatory mediators this leads to pain, including substance P, histamine, encephalin, dopamine, serotonin, glycine, GABA, Prostaglandin E, leukotrienes and cytokines.[39] Furstman concluded that pain results from a combination of pressure, ischemia, inflammation, and edema.[45] In an experiment evaluating

orthodontic tooth movements in cats, the levels of substance P in the pulp increased dramatically at around three hours following orthodontic force application in the pulp, and at 24 hours in the PDL.[46] Substance P is a neuropeptide released from nociceptors in the region of tissue damage causing the pain receptors in the area to increase their rate of firing.[47] Ngan suggests that his and others' findings support the idea that orthodontic pain following insertion of separators or arch wires is related to rising levels of prostaglandins and substance P in the peridontium.[12]

Krishnan and Davidovitch characterize orthodontic force as resulting from the abrupt creation of compression and tension regions within the periodontal ligament. Force-induced strains lead to changes in the blood flow in the periodontal ligament, resulting in the synthesis of molecules such as neurotransmitters, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites.[18] A distinction has to be made between the slow process of physiological tooth movement, contrasted with orthodontic tooth movement, which is some ways is force-dependent in the sense that the rate of movement depends on characteristics of the applied force as well as the size and biologic response of the periodontal ligament.[48]

Orthodontic Force Magnitude, Necrosis and Pain

Textbooks state that the response to sustained force against the teeth is a function of force magnitude, that heavy forces lead to rapidly developing pain, necrosis of cellular elements within the PDL and the phenomenon of undermining resorption, and that lighter forces are compatible with survival of cells within the PDL and a remodeling of the tooth

socket by a relatively painless 'frontal resorption" of the tooth socket.[2] It is also believed that tooth movement is more efficient when areas of PDL necrosis are avoided, and that pain is also lessened.[2] In 1971, Gianelly and Goldman argued that while every orthodontic appointment involves some degree of pain, higher force levels equaled greater periodontal compression and therefore more pain.[49] It is a common assumption in the practice of clinical orthodontics that the use of lighter forces to elicit movement of teeth is preferable to the use of heavy forces. This is mainly due to the orthodontist's compassionate concern for the patient's pain. Krishnan and Davidovitch state that optimum force should be viewed as an extrinsic mechanical stimulus that evokes a cellular response that aims to restore equilibrium by remodeling the periodontal supporting tissues; the mechanical input that leads to the maximum rate of tooth movement with minimal irreversible damage to the root, PDL, and alveolar bone is considered optimal.[48] The ideal force magnitude then, should be capable of producing a maximal rate of tooth movement without a compromise in patient comfort. Burstone describes an optimal force as one that produces a rapid rate of tooth movement without discomfort or ensuing tissue damage (particularly alveolar bone loss and root resorption). From a histologic viewpoint, an optimal force is one that produces a stress level in the PDL that basically maintains the vitality of the tissue and initiates a maximum cellular response (apposition and resorption). Optimal forces produce direct resorption of the alveolar process. Because optimal forces require no period for repair, they apparently can be made to act continuously.[50]

It has been postulated that when the blood supply in the periodontal ligament is completely occluded in the presence of heavy pressure, the resulting signaling molecules

and greater necrosis may play a role in the way pain is experienced by the patient. Burstone states, without providing supporting evidence, that not only is a greater degree of pain evident with heavier forces, the total number of days that the abnormal pain response is elicited is also higher.[3] Proffit agrees, stating that there does seem to be a relationship between the amount of force used and the amount of pain: the greater the forces, the greater the pain, all other factors being equal. This is consistent with the concept that ischemic areas in the PDL are the major pain source, since greater force would produce larger areas of ischemia.[2] If orthodontists subscribe to these ideas, they may seek to apply forces to teeth that limit the amount of undermining bone resorption that occurs. Proffit contends that light forces are the key to minimizing pain as a side effect of orthodontic treatment.[2]

In what Proffit describes as the modern "soft-tissue paradigm", it is generally accepted that positions of teeth are influenced by the musculature in the lips, cheeks and tongue. An interruption of the relative equilibrium results in tooth movement. It is known that appliances such as the lip bumper allow the movement of teeth by disrupting the pressure equilibrium in the oral cavity. Teeth not in physical contact with the appliance move, without pain. Although very light, the forces derived from the positions of the tongue cheeks, and lips contribute to the positional changes of the teeth. It therefore can be assumed that very light forces with a long enough duration are effective at moving teeth without pain. At the other end of the magnitude spectrum, we know that heavy forces are also effective at moving teeth. Brass separators work, as do brackets tightly ligated to heavy rectangular steel archwires. Anyone in the practice of clinical orthodontics who has inserted a .019 x .025 retraction archwire with an appreciable

amount of torque in the incisor region has seen firsthand that orthodontic adjustments can cause patients a considerable amount of immediate discomfort. In some cases, patients complain of pain while still in the dental chair. In other cases, patients do not report discomfort until approximately six hours later. This indicates there is a large range, or spectrum, of pressure levels that are effective at moving the roots of teeth through bone. Although specific instances of the significance of pain in orthodontics will be discussed later, for the moment, it seems self-evident that as compassionate healthcare practitioners, orthodontists should be interested in finding the place along this force spectrum that minimizes the experience of while still maintaining effectiventooth movement. However, there exists disagreement over whether this is even possible. In 2006 in the American Journal of Orthodontics, Krishnan and Davidovitch concluded that inflammation of paradental tissues occurs every time they are exposed to an orthodontic force, whether the magnitude is light or heavy.[48] As Oesterle et al. point out, force levels might be more of art than of the science of orthodontics, with the art having a strong historical background.[51] Jones and Richmond go further by stating that force levels should not be considered a significant factor relative to pain. Evaluating the relationship between initial tooth positions, applied force levels, and pain, they found no differences when measuring the amount of deflection of the archwire. They concluded that the amount of displacement of the archwire could be inferred as a higher force level and their lack of results indicated that force levels were not important.[32]

When the pressure is light enough to not completely occlude the blood vessels, the locally derived osteoclasts resorb the lamina dura. Reitan used light wire torque in human premolars and concluded that 50g led to “direct” or frontal resorption of bone.[1] It

is thought that when forces are higher, however, and the vasculature becomes completely occluded, that sterile necrosis occurs within the PDL rather than differentiation of local cells into osteoclasts. Reitan showed in dogs that a force magnitude of 400g caused what was called semi-hyalinization on the pressure side of all teeth.[1] Hyalinization is a term that may be used interchangeably with aseptic ischemic necrosis, as it indicates cellular death resulting from lack of a blood supply. In a 2004 study of beagle dogs, Bohl et al. showed a definite relationship between the development of hyalinization zones and force magnitude; higher forces consistently caused more areas of hyalinization.[52] In a split mouth design, they applied a constant reciprocal force of 25g on one side of the mouth and 300g on the other. The increased force levels were associated with more hyalinization but had no effect on the rate of tooth movement, although large variation in displacement per unit time was evident between individual dogs.[52] In a separate study, Bohl et al. showed focal hyalinization that limited tooth movement when light forces were applied.[53] Rather than frontal resorption occurring and tooth movement beginning soon after force initiation, osteoclasts must be recruited from the bone marrow spaces and resorption occurs from the side of the lamina dura opposite the PDL. This is known as undermining resorption. Because more bone must be removed before there is space for the tooth to move, the teeth proceed in a stepwise fashion following a delay of several days during which no movement occurs. Burstone describes three phases of tooth movement: the initial, lag, and postlag phases.[50] The initial phase is a period of rapid movement that tapers off around the sixth day, after which tooth movement comes to a relative halt. Reitan suggests that non-vitalization of the PDL is responsible for this.[1] Storey and Smith have advised that until the removal of these non-vital areas occurs,

further tooth movement is not possible.[8] Owman-Moll et al. confirmed the efficacy of light forces, showing that when undermining resorption occurs, the rate of tooth movement does not increase.[54] Bohl et al. concluded, conversely to Storey and Smith, that while the appearance of necrotic tissue may be related to force levels, this does not affect tooth movement.[52]

Histological studies based by Reitan and Storey were the first to suggest a connection between higher degrees of avascular necrosis, heavier forces, and a more painful orthodontic experience.[55] Storey and Smith suggested in 1952 an optimum range of pressure between 150 and 200 grams for cuspid retraction.[55] They showed that lighter than optimal force failed to produce movement, and that at greater forces, rates of tooth movement decreased and then fell to zero within a week. Ogura et al. performed an experiment where individual premolars were intruded with forces of 20 and 200 cN (about 20 to 200g). No differences were reported in spontaneous pain. From the time period of 8 to 100 hours, however, there was a significant difference between pain when the teeth were subjected to biting forces, which is reasonable considering that the force was being applied in the direction of the line of action.[56] However, not all studies agree that force levels and pain are related. Boester and Johnston investigated the use of different force levels during retraction of canines in first premolar extraction cases.[57] In ten patients who had each of their four quadrants subjected to force levels of 2, 5, 8, and 11 oz (55 to 310 grams). Pain levels were estimated by recording whether patients complained. Subjects were asked to recall at the end of each week which quadrants had been uncomfortable. There was no relative measure of pain intensity. There were no significant differences in discomfort levels, though the lowest force levels elicited the

fewest complaints. A key finding was that although the three higher force levels produced equivalent movement, the lightest force produced significantly less movement, suggesting there may be a range between 2 and 5 oz (55 and 140 grams), that produce a maximal rate of tooth movement. A study conducted by Andreasen, which compared forces of between 100-150g on one side to forces of 400-500g on the opposite side concluded that force levels and pain are not related.[58] Erdinc et al. also found no differences between patients who began treatment with either a .014 or an .016 NiTi wire. However the force levels delivered by the two wires used were not determined, so interpreting this as meaning force is not important may be more problematic than for previous studies that measured force directly.[25] A 1985 study by Jones and Richmond also failed to find a relationship between magnitude of force application during initial tooth movement and amount of pain.[32]

Krishnan and Davidovitch stated that to effect orthodontic tooth movement, only 20 to 150 grams of force per tooth is necessary.[48] Such force levels are sufficient to alter blood flow and upset the homeostatic environment of the periodontal ligament. They contend that to engender adequate biological response in the periodontium, light forces are preferable because of their ability to evoke frontal resorption of bone. Heavy forces on the other hand, have been implicated in root resorption, and are known to often cause necrosis in the PDL and undermining bone resorption.[48] Additionally, according to Krishnan and Davidovitch, it is impossible to measure precisely the amount of force applied to roots or parts thereof under any mode of treatment.[48]

Of course, it is probably not possible to eliminate the pain experienced during orthodontic treatment for all patients. Even with lighter forces, there will always be an

uneven distribution of forces within the PDL producing small areas of complete blood vessel occlusion.[50] Similar noxious stimuli may affect various individuals to widely varying degrees. Individuals vary widely in both their pain thresholds and pain tolerances. Pain, while it is universally unpleasant, is a subjective, individual experience with many contributing factors, which will be discussed in more detail later. Much has been written on how heavier force levels cause a different biological effect than lighter forces, namely causing undermining bone resorption. It has been proposed that this is chiefly a product of the amount of total occlusion of blood vessels in the periodontal ligament. The idea that a lighter force only partially occludes blood vessels in the periodontal ligament and is effective in moving teeth via the process of frontal resorption sounds good in theory, but it is unlikely that this process could occur in the complete absence of any undermining resorption when an orthodontic force is applied. Extremely light forces as low as 10 grams have been shown to be capable of simple tipping.[10] However, Bohl et al. showed that even very light orthodontic forces are not distributed equally throughout the PDL, possibly due to irregularity of the anatomy of the PDL and bone morphology, cause focal hyalinization points that limit tooth movement.[53]

Treatment and Its' Effect on Pain

Many studies have attempted to identify what the orthodontist may be able to do from a treatment perspective to reduce the amount of pain experienced by the patient. The design of these studies have usually involved testing one treatment method against another. At the initiation of orthodontic treatment, pain intensity follows a predictable

pattern, appearing around four hours after insertion, peaking at around 24 hours and usually resolving after 7 days.[47]

Krukmeyer et al. explored whether orthodontists were able to accurately assess their patients' levels and experience of pain during orthodontic treatment, and also whether they were aware of their patients use of analgesics.[15] In a survey of 116 adolescents and their providers, they found that orthodontists underestimated both.

Jones and Chan found that the prevalence, intensity, and duration of pain were not statistically significantly different when comparing a Twistflex steel archwire to a nickel-titanium; they also found no differences in pain between the dental arches.[8] In their study the pain score peaked on the morning after placement of the archwire and lasted for a total of 5-6 days. The pain intensity versus time curve for placement of the second archwire in this study was almost identical. In comparison to extractions of premolars in the same patients, pain was greater for archwire placement and was of greater duration. They also found that the degree of initial crowding did not have an effect on the amount of pain reported. Evaluating oral discomfort using a lingual technique, Weichmann confirmed the findings that the degree of malocclusion measured on the casts failed to predict the amount of discomfort experienced by the patient.[59]

Tuncer et al. used a VAS to compare pain reported after placement of initial archwires to the pain reported when using intermaxillary elastics.[60] Pain was experienced as soon as two hours following the application of intermaxillary elastics; it peaked after approximately 6 hours, and began to decrease two days later.[60] Although the amount of discomfort experienced with elastics was similar to that of archwires, the pain did not last as long as the pain felt from the initial bonding. The patients who reported

noncompliance with elastics reported severe pain. Elastics were chosen to deliver 15 grams of force to the teeth and were either in a Class II or Class II configuration. The authors noted the significance of this as most clinicians tend to ignore the patient's discomfort and blame extended treatment time on the patient.[60]

Pringle et al. used a VAS to evaluate self-reported pain during the first 7 days of treatment.[61] They compared two fixed bracket systems produced by Ormco, the Tru-Straight and the Damon 3, both using a .014 inch super-elastic nickel-titanium archwire. Pain intensity levels were recorded twice per day, and use of analgesics were also monitored. Pringle reported that the mean maximum pain intensities were 40.92 mm (n=24; 95% CI, 30.40-51.44 mm) for the Damon 3 patients and 55.71 mm (n=28; 95% CI, 45.93-65.50 mm) for the Tru-Straight patients. After controlling for coviariates, the mean difference in maximum pain intensities was 11.77 mm. Although not significant with a $P > .053$, the clinically relevant difference in the sample size calculation was 20 mm, sugggesting that the difference is unlikely to be clinically significant. In this study there was no significant difference in mean maximum pain intensity as a result of irregularity as measured by Little's irregularity index. Pringle et al. noted that the patients could have been biased by the more modern appearance of the Damon 3.[61] Slightly more than half the patients took oral anagesics.

Scheurer et al. compared the pain scores from three appliances: a 2x4 appliance, a full fixed appliance of one arch, and full appliances in both arches and found no differences in pain frequency, intensity, or analgesic consumption.[7] It is surprising that the number of teeth bonded to the appliances had no measurable effect on the intensity of pain reported. Consistent with other studies, pain intensity peaked at 24 hours and

steadily decreased over the course of seven days. Percentages of patients consuming analgesics were 16% on the second day. Patients younger than 13 reported pain less frequently older patients.

Fleming et al. also studied the self-reported pain experience of patients during the initial archwire phase of treatment by comparing self-ligating brackets to conventional pre-adjusted twin brackets.[62] They used a .016 inch nickel-titanium archwire. This study found no difference in pain during the first week of treatment between bracket types. Pain peaked on the morning after placement of the archwire and remained at this level for 2 to 3 days before mostly resolving at 5 to 6 days.[62] Fleming et al. used a sample size of 46 participants, which was proposed to offer 80% power at a 95% confidence interval, to demonstrate a difference of 10 mm in the VAS score. The study found that 60% of patients required analgesia, which the authors indicated highlights the severity of orthodontic pain.[61]

Nalbantgil et al. used the VAS to compare pain perception associated with elastomeric separators and brass wire separators.[29] The elastomeric separators produced more separation than brass wire separators. Although the brass wire separators were more painful immediately after placement, at every other time point patients experienced more discomfort from the elastomerics, which caused significant discomfort for up to a week.[29] For the separators, the discomfort was measurable within 4 hours of placement, increased for the next 24 hours, and then decreased to pre-placement levels by 7 days. No differences were found between men and women in their perception of pain.[29]

Bergius et al. studied adolescent patients who received elastic separators and were divided into two groups based on whether they still felt pain after seven days.[47] Intensity

was measured on a VAS. The purpose of the study was to identify factors that could predict prolonged pain experience during orthodontic treatment. More than 40% of patients reported pain after one week of follow up. In the adolescent group, girls reported pain more often and of higher intensity. Twenty-five percent of patients reported taking analgesics, and among those patients, pain scores were higher.

Otasavic et al. investigated the pain experienced during the first week of initial archwire application, comparing patients who avoided mastication to those who used a bite wafer, and found that the bite wafer group experienced more pain.[13] All patients' initial archwires were .016 inch nickel titanium. Patients in the reduced mastication group were instructed not to masticate for three hours following placement, and to avoid hard food for a week. Patients in the bite wafer group performed supervised mastication for 10 minutes immediately following placement and were instructed to chew on the wafers daily for the next seven days. Analgesic consumption peaked at 10% of patients on the first day. This paper was later contradicted by Murdock et al., who found that relief from bite wafers were comparable to oral analgesics.[63]

Ngan et al. used a VAS in order to characterize the pain experienced by patients receiving either separators or initial archwires.[12] Their results suggest that inflammation of gingival and periodontal tissues could lower pain tolerances due to hyperalgesia, which can be initiated by prostaglandins.[12] Ngan used the VAS to measure pain, noting that it was better than a verbal descriptor scale when performing successive measures during treatment.[12] In this study, pain started to increase 4 hours after placement of either a separator or an archwire, peaked at around 24 hours, and subsided mostly by 7 days. Of the 24 male subjects and 41 female subjects, no significant difference was found between

the sexes with either separators or archwires. Also, no significant differences were found between those older and younger than 16 years of age. Although no significant differences were found between separators and archwires, both showed a significant increase in pain during chewing and biting versus baseline.[12]

Erdinc and Dincer compared the pain reported by boys and girls when initial archwires of .014 and .016 inches were randomly placed. Pain was present at 2 hours, peaked at 24 hours and decreased by the third day. No significant differences were found between sexes or the two archwires.[25]

Relief of Pain

According to Krishnan, the existing literature supports the routine use of NSAIDs for pain control and suggests that at low doses, they will not affect the tooth movement process.[39] Polat showed that two to three doses of an NSAID were effective in reducing pain following the placement of fixed appliances.[64] Ngan et al. compared ibuprofen, aspirin, and placebo and concluded that ibuprofen was superior.[65] They state that the current trend is for medication to be given at least one hour prior to all orthodontic procedures. In 2006, Young et al. evaluated the effect of timing on Valdecoxib therapy and showed patients experienced no increase from baseline when given 40 mg at least thirty minutes prior to initial archwire placement. Pain was significantly less than for those who received the same drug following placement, which reduced pain by about half when compared with placebo.[64] Fleming et al. also recommended the use of preemptive analgesics, due to NSAIDS comparative inability to adequately control orthodontic pain

after treatment has begun.[62] Although analgesics are recommended, their effect on reported pain intensity is hard to determine. Various studies found that higher pain scores were found in patients who consumed analgesics.[25,7,14] Results from a study by Pringle et al. comparing two different bracket types (self ligating vs. twin) further supported these findings.[61] One might expect that patients who use pain medication would find relief and report lower scores, but research does not support this assumption.

Invisalign

The first reports of clear aligner therapy date back to 1945, with the work of Kesling.[66] At the time, individual gypsum setups were produced by hand for each minor tooth movement and thermoplastic trays were fabricated that mimicked the stages of tooth movement. Though Kesling understood that the technology of his era did not make comprehensive treatment feasible due to the tremendous amount of manual labor and cost that were required, he did predict that it would one day be available. Later, Raintree Essix created appliances limited to 2 to 3 mm of tooth movement using windows in the appliances. Align technology introduced the Invisalign system allowing comprehensive Orthodontic treatment with the ability to stage a virtually unlimited number of stereolithographic models based on computer software. Kwon et al. described the mechanism as force being delivered to the tooth as the plastic overlay returns to its original state.[67] Raintree Essix contends that the ideal distance per tray is between .5 to 1.0 mm. Align uses .25 mm and determines the number of trays needed for a treatment plan by a computerized calculation based on the tooth that must move the furthest

distance throughout the course of treatment.[68] In essence that tooth is the rate limiting step. The other teeth move various distances per tray based on the total distance they are required to move throughout treatment. Typically it is recommended that a patient wear aligners for a period of two weeks.[67] Boyd et al. published the first paper on Invisalign and was involved with the earliest treatment of patients at University of the Pacific.[68] At the time they stated that the treatment is sequenced into a series of evenly divided .15 to .25 mm movements.[69] The variation is explained by the fact that not all teeth are required to move the same distance over the course of a treatment plan. Prior to forming, the plastic material used by Invisalign is .030 inches or approximately 0.75mm thick.[69]

Kwon et al. investigated various thicknesses of various thickness of Essix plastics and compared forces delivered in vitro on a proprietary 3 point bending device.[67] They noted that there was variation among the types of plastics, thicknesses of plastics, and distance deflected to achieve an "ideal" force. In general the distance of deflection varied from .2 to .5 mm. The values for these ideal force levels are based on suggestions from Proffit's Contemporary Orthodontics which are 35-60g for tipping and 70-120g for translation.[2] These are values based on the clinical experience of an expert rather than actual research, although they may have their origins in the work of Storey and Smith and Boester and Johnston.[55,57] In 2009, Hahn et al. performed another in vitro study with three types of thermoplastic materials called Erkodur, Biolon and Ideal Clear, using a device that measured what he called all six components of forces and moments.[70] Tipping forces ranged from 282 to 542 g for deflections of .151 mm. They concluded that the forces were mostly too high when compared with those stated in the literature as ideal. Hahn and coworkers note that the measuring device does nothing to simulate the

periodontal ligament and stated the clinical significance of their measurements is not yet established. They sharply criticized results published by Kwon et al., who detected lower force levels because they used a much less sophisticated three point bending setup. Hahn et al. claimed that such a device is not useful for simulating the force delivery properties of thermoplastic orthodontic appliances.[71] It should be noted that a deflection range of .151mm is considerably less than Align's .25 mm default, and that even at this low range forces for tipping are 5 to 11 times higher than those recommended by Proffit.[71] No investigations of this type have been undertaken using Align's proprietary plastic. It also should be noted that the increments per tray used by Invisalign is an important aspect in the development of the appliance because it reflects the maximum amount of activation possible, given the virtual tooth position, modulus of elasticity of the appliance material and thickness.[69] Align's primary focus would have been the modality's effectiveness rather than finding the lowest possible deflection to move teeth if the founders hoped to be successful as an orthodontic company. It would make sense to engineer a tray that had more than enough force to initiate the biological response in the PDL, especially considering the fact that overall effectiveness may have been reduced by the fact that the appliance is removable and therefore subject to patient compliance. However, Boyd et al. noted in 2001 that the forces involved are most likely light and continuous considering tray elasticity and the relatively small amount of activation.[69] These conclusions are the opinions of an expert however, and do not agree with the in vitro studies by Hahn et al.[71] Interestingly, Align technology recently issued a press release to their stockholders indicating that the next "generation" of aligners would use a new type of plastic called SmartTrack, which they claim is more resilient and capable of delivering gentler forces.[72]

Nedwed and Miethe conducted the first study that surveyed Invisalign patients regarding their difficulties with treatment, including their pain experience.[73] The survey involved 12 questions of patients who were 3 to 6 months into treatment. The question on pain was a verbal descriptive scale with "no, minimal, or severe" the possible answers. 35% of the patients reported no pain, 54% reported minimal pain, and 11% reported pain as severe. The limitations of verbal descriptive scales have previously been discussed. Importantly, the choices did not offer a descriptor for "moderate" pain, thereby forcing patients to choose between minimal and severe pain, which may have biased the results toward "minimal". Asking patients who were at least 3 months into treatment to recall a pain experience is less reliable than questioning them by diary at the time of experience.[12]

Perhaps the best study to date regarding pain and Invisalign was conducted by Miller et al. in 2007.[28] Their purpose was to evaluate the differences in quality of life impacts of Invisalign versus fixed appliance therapy during the first seven days of treatment. Miller and colleagues showed that Invisalign patients experienced less pain at each of 7 time intervals. Though the Invisalign patients had returned to baseline by day five, the mean pain scores for patients in fixed appliance therapy were still above baseline on the end of the seven days. Pain peaked 24 hours after placement. The group receiving fixed appliance therapy also consumed significantly more pain medication for the first three days, and reported more negative functional and psychological effects.[28]

Shalish and colleagues compared the pain experience during intial insertion of fixed buccal, fixed lingual, and Invisalign appliances. They found no statistically significant differences between the appliances, but did report that the highest number of individuals reporting severe pain on the first day were in the Invisalign group, and

concluded that this may have been due to the heavy forces placed on teeth by the aligners early into treatment.[74] This is opposite from the findings of Miller et al. Shalish and coworkers hypothesized that this may have been due to the greater mechanical force of the Invisalign appliance early in treatment, whereas those in the fixed buccal group received a lighter, more continuous force applied to the teeth.

Because Invisalign is a removable appliance, a patient enjoys a greater amount of control over the application of force to the teeth. A patient's perception of their discomfort may be lessened by knowing they have the ability to remove the appliance at will. The ability to control or influence a situation has been suggested to reduce the experience of both stress and pain.[19] The current study will be examine the Invisalign appliance and varying the amount of tooth movement per tray. Though orthodontists have much control over force levels with full fixed appliances, it is less obvious whether orthodontists can exert similar control over their treatment plan with aligners. Many orthodontists realize that they can prescribe specific tooth movements in terms of tip, torque, and rotation, and can apply their understanding of the proper order of treatment mechanics from their experience using fixed appliances. Little attention has been given to what the orthodontist can do in terms of rate of tooth movement. The initial patient records provide the start point, and through the process of the ClinCheck®, the orthodontist and the technician agree on the end point (and thus the distance the teeth will move), but the number of aligners and times that the patients change them are determined by Align. Align determines which tooth will need to move the furthest distance over the course of the treatment plan and designates it as the "lead tooth". By default, this tooth will move .25 mm per tray, and the movement of this tooth determines the number of

aligners. Though this amount of movement is not unreasonable, it is arbitrary.[19] The current study will examine if adjusting the amount of movement per tray, thereby affecting the amount of pressure placed on the teeth could lead to a decrease in the amount of pain reported by patients undergoing orthodontic treatment with the Invisalign appliance. Theoretically, as one increases the number of aligners, it should be possible to eventually find an increment small enough that it is incapable of producing orthodontic tooth movement. Subsequently, if one were to begin inserting trays in succession, it should be possible to locate an increment that produces just enough force to produce tooth movement with the lightest force necessary. The current study reduces the increment by half. Although the study by Hahn et al. was not based on the plastic used by Align, his calculations that the force levels were five to eleven times higher than ideal indicate that even by halving Align's default increment, force levels may still remain too high.[70] However, it would be a mistake to assume that reducing the increment by half would only reduce the force levels by half. No studies have been performed that provide information about this relationship. However, it should be clear that a smaller incremental distance might be expected to produce less deflection of the aligner and apply less pressure to the teeth.

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Chapter 3: Journal Article

Abstract

Purpose: To compare the effects of halving the incremental distance of Invisalign® (Align Technology, Santa Clara, California) aligners, while maintaining the overall distance of tooth movement. **Materials and Methods:** A prospective, partially randomized longitudinal trial evaluated 38 patients in private practices prior to treatment, and at 6 hours, 24 hours, 2, 3, 7, 8, 9, 14, 15, and 16 days after placement of aligners. Approximately half the patients followed the default schedule suggested by Align by wearing their aligners for 14 days. The experimental group received aligners prescribed to move the teeth half the default distance, but changed their aligners every week. The total distances the teeth were prescribed to move were the same in both groups. The level of discomfort was measured using questionnaires and a Visual Analog Scale (VAS). **Results:** Discomfort increased initially and peaked at 24 hours, with no significant group differences in median discomfort scores during the first seven days. After they changed to their second aligner at eight days, patients in the experimental group reported significantly ($p<.05$) more discomfort than those in the traditional group. Patient in the traditional group reported almost no discomfort at eight days. At 14 days following insertion, when the traditional group changed aligners, they experienced significantly more discomfort than the experimental group, who had not yet changed their second aligners. There were no significant differences in the amount of discomfort reported by the experimental group at 8 days and the traditional group at 14 days. **Conclusions:**

Patients following the traditional Invisalign® protocol in which teeth are prescribed to move .25 mm every 2 weeks do not experience more discomfort than patients whose trays are prescribed teeth to move half that distance and whose trays are changed twice as often.

Introduction

One of the most important factors deterring people from seeking orthodontic treatment is the fear of pain.[1] Approximately 90% of patients report experiencing pain during orthodontic treatment and approximately one third of them think about ending treatment prematurely due to pain.[1] Pain is also a major factor explaining missed appointments and a primary reason for noncompliance, including oral hygiene.[2] Tayer et al. found pain to be the most discouraging part of orthodontic treatment among adults.[3] It has been reported that up to 8% of patients discontinue treatment due to pain, which might be expected because pain causes withdrawal from situations.[4] The nervous system detects and registers perception of unpleasant sensations in order to protect individuals from physical harm or the potential thereof. The body recognizes pain first through nociception, defined as the neural processes of encoding and processing noxious stimuli.[5]

According to Levine and Reichling, inflammation is the single greatest cause of pain; pain involves various mechanisms by which chemicals sensitize and increase the activity of neurons responsible for communicating pain signals.[6] Inflammation can isolate the site of injury and protect the organism from further damage; the process is also

responsible for the removal of damaged tissue and the orchestration of local repair.[6] Various inflammatory mediators are directly responsible for hyperalgesia, the state where a painful stimulus may result in an unexpectedly high level of pain, including prostaglandins, leukotrienes, serotonin, adenosine, histamine, interleukin 1, interleukin 8, and nerve growth factor.[6,7,8,9]

Orthodontic forces are known to produce mechanical damage and inflammatory reactions in the periodontium, causing an increase in levels of many inflammatory mediators.[7,10,11] Prostaglandin E is important for its unique ability to stimulate both osteoblasts and osteoclasts, the cells responsible for bone remodeling during tooth movement, and is known to cause pain.[11] Orthodontic force application raises levels of inflammatory mediators that lead to pain, including substance P, histamine, encephalin, dopamine, serotonin, glycine, GABA, Prostaglandin E, leukotrienes and cytokines.[12]

Textbooks state that heavy forces lead to rapidly developing pain, necrosis of cellular elements within the PDL and undermining resorption, while lighter forces produce less cellular necrosis and remodel the tooth socket by relatively painless frontal resorption.[11] In 1971, Gianelly and Goldman argued that higher force levels equaled greater periodontal compression and therefore more pain.[13] The notion that increased compressive forces produce greater pain is based on histologic studies showing greater areas of hyalinization associated with higher force levels.[14] More recent research indicates that pain, as reported by patients, is not greater with higher force levels.[15,16,17,18] Nevertheless, orthodontic companies continue to advertise products claiming more comfortable experiences for patients due to lighter forces. Align technology recently issued a press release indicating that the next "generation" of aligners would use a new

type of plastic called SmartTrack, which they claim is more resilient and capable of delivering gentler forces.[19]

Several in vitro studies have attempted to characterize the force levels delivered to teeth by thermoplastic appliances. Kwon et al. were among the first to describe the forces being delivered to the tooth as the plastic overlay returns to its original state.[20] Interestingly, an in vitro study of three thermoplastic materials showed that deflections of .151 mm produced 282 to 542 g of tipping forces. [21] The .151mm deflection reported by Hahn et al. is considerably less than Align's .25 mm default, suggesting that Invisalign forces may be higher than those recommended for tipping .[22] The .25 mm increment used by Align is arbitrary, but it is clearly related to force magnitude delivered to the teeth.[23] Importantly, only one study has evaluated pain experienced by Invisalign patients, and it showed that patients experience significantly less pain from Invisalign than from fixed appliances during the first 7 days of treatment.[24] More studies are clearly needed to understand the relationship between force levels and pain, especially for Invisalign patients.

The current study is the first to vary force levels within the Invisalign treatment modality and relate them to pain. It will determine if reducing the amount of movement per tray, thereby reducing the amount of pressure placed on the teeth, decreases the amount of pain reported by patients undergoing orthodontic treatment with Invisalign® appliances. Theoretically, as one increases the number of aligners, it should be possible to identify an increment that produces just enough force to produce tooth movement with the lightest force necessary. The current study reduces the increment by half. The purpose of the study was to evaluate whether aligners that move the teeth a smaller

distance reduce the amount of discomfort experienced by patients. No studies have previously evaluated this relationship.

Materials and Methods

A prospective, partially randomized sample of 38 Invisalign® patients were evaluated 6 hours, 24 hours, 2, 3, 7, 8, 9, 14, 15, and 16 days after placement of their aligners. The time points during the first week were selected based on previous studies showing predictable pattern of discomfort from orthodontic treatment, and during the second week to coincide with aligner changes.[17,24,25,26] The level of discomfort was measured using a 100 mm long Visual Analog Scale (VAS).

Thirty-three patients were drawn from a private practice in Virginia, five patients came from a private practices in California, Missouri, and Virginia. Twenty-two patients (14F, 8M) followed the traditional protocol recommended by Align and changed their aligners every two weeks. Sixteen patients (11F, 5M) followed the experimental protocol that required them to change their aligners changed weekly, with each expressing half the traditional distance per tray. The groups were similar in terms of percentages of women versus men and mean age (22.5 years of age for the traditional group and 23.1 years for the experimental group). Fourteen patients, six of whom were following the experimental protocol, enrolled in the study but failed to return surveys. The office from which the majority of the data was collected only began randomization following recruitment of three subjects who had previously been treatment planned for the

traditional protocol. Another office who agreed to participated in the study recruited 7 patients but did not assign any to the experimental protocol. Only one subject from this office returned a survey.

Only patients who had been approved for Invisalign as an appropriate treatment modality were asked to participate in the study. Informed consent was obtained from each patient and the study was approved by the Saint Louis University IRB committee. Each patient filled out a survey asking them about their levels of discomfort at various time points during their first two weeks of treatment. They were informed that they would randomly be placed into one of two groups and that their treatment plan may be altered as a result. Blinded treatment coordinators in each of the private practices were responsible for assigning the patients to either the green (experimental) or blue (control) groups, and were asked to allocate men and women separately to maintain parity. Orthodontists were instructed to treatment plan cases normally. If, prior to final approval of the Clincheck, the patient had been assigned to the "green" group, the orthodontist requested that Align double the number of aligners. If an orthodontist specifically planned reduced velocity of tooth movements due, it was allowed for either treatment group. Orthodontists were instructed to not place attachments for the duration of the study. No interproximal reduction was performed during the first two weeks of treatment in order to eliminate sensitivity due to reduction of enamel. Patients who required daily pain medication for any condition were excluded. Subjects in the experimental group were instructed to change aligners after 7 days. Subjects in the traditional group were instructed to change their aligners after 14 days. The overall velocities of tooth movement in both groups were the same over the course of treatment.

Survey Instrument

On the day that their first aligners were delivered, subjects were provided a survey that was either printed on blue or green paper, along with written instructions and a pre-addressed stamped envelope for returning the survey. The blue and green colored surveys were identical, except for the instructions on when they were supposed to change to the next aligner. The first page of the survey consisted of two questions that the patients answered prior to treatment pertaining to 1) the worst pain they had ever experienced and 2) their level of discomfort immediately prior to receiving the aligners. The remaining pages consisted of sets of five questions that were answered at each time point. Two questions pertaining to discomfort at rest and discomfort when chewing were answered using a 100 mm long VAS. Among techniques to measure pain in patients, the VAS is established as the most accurate and reliable. It is the most commonly used numeric scale at present.[27] It is more sensitive than the verbal descriptor scale when considering successive responses to treatment.[28] There is high correlation between successive measurements of pain severity.[29] The other three questions were yes/no questions asking whether the patient 1) had removed the aligners due to discomfort, 2) had taken medication to relieve tooth discomfort, or 3) had taken medication to relieve any other type of discomfort. Subjects returned the survey via a stamped envelope that was supplied.

Statistical Analyses

Preliminary analyses showed that many of the variables' distributions were significantly ($p<.05$) skewed and kurtotic. Due to skewness and kurtosis, medians and interquartile ranges were used to describe the results and the Mann-Whitney-U analysis was used to test group differences.

Results

Pain increased significantly (prob < .05) 6 hours after insertion of the first aligners in both groups, peaked at 24 hours and decreased over the next six days (Table 3.1 and 3.2; Figures 3.1 and 3.2). There were no significant group differences in median pain scores during the first seven days. Pain scores while chewing were consistently higher than pain scores at rest, but they followed the same temporal pattern, with no significant group differences over the first seven days.

Table 3.1 Medians and interquartile ranges (IQR) of pain when asked " My level of discomfort generally is:" along with the differences at each timepoint evaluated with the Mann-Whitney U test.

Time	Traditional		Experimental		Difference	Mann-Whitney U
	Median	IQR	Median	IQR		
6 hours	9.0	2.9 – 24.3	9.8	0.4 – 22.1	-0.8	.824
1 day	18.8	11.9 – 43.1	16.6	8.1 - 28.7	2.2	.322
2 days	7.0	1.2 – 18.3	9.4	0.8 – 21.4	-2.4	.689
3 days	3.8	0.0 - 20.9	4.5	0.0 - 10.2	-0.7	.716
7 days	0.5	0.0 - 11.8	0	0.0 - 12.5	0.5	.500
8 days	0.3	0.0 - 6.2	12.4	0.2 - 24	-12.1	.012*
9 days	0.0	0.0 – 4.0	4.3	0.0 - 19.1	-4.3	.097
14 days	18.4	6.2 - 27.7	0	0.0 - 8.8	18.4	.002**
15 days	11.1	3.5 – 34.9	0	0.0 - 15.8	11.1	.09
16 days	5.8	0.0 - 17.1	0	0.0 - 17.7	5.8	.197

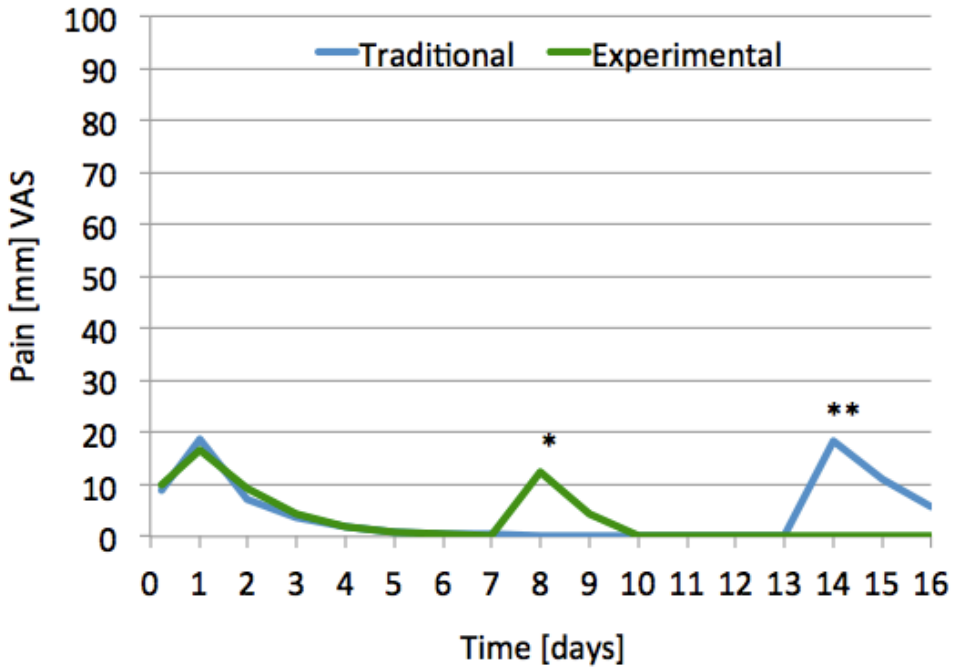

Figure 3.1. Pain, measured with a visual analogue scale (VAS), reported by Invisalign® patients when asked "My level of discomfort generally is:" [* indicate significant (p<.05) group differences, ** indicate significant (p<.01) group differences].

Table 3.2 Medians and interquartile ranges (IQR) of pain when asked " My level of discomfort while chewing is:", along with the differences at each timepoint evaluated with the Mann-Whitney U test. [* indicate significant (p<.05) group differences, ** indicate significant (p<.01) group differences].

Time	Traditional		Experimental		Difference	Mann-Whitney U
	Median	IQR	Median	IQR		
6 hours	19.1	0.0 – 31.7	8.4	1.0 – 34.9	10.7	.976
1 day	27.1	13.9 – 43.3	18.0	11.3 – 37.6	9.1	.225
2 days	8.5	0.0 – 28.6	4.8	0.0 – 29.0	3.7	.876
3 days	3.4	0.0 – 20.9	4.3	0.0 – 19.1	-0.9	.951
7 days	0.4	0.0 – 10.2	0.0	0.0 – 14.0	0.4	.627
8 days	0.0	0.0 – 7.6	18.1	0.0 – 25.4	-18.1	.045*
9 days	0.0	0.0 – 5.9	4.9	0.0 – 16.8	-4.9	.087
14 days	12.2	3.4 – 30.4	0.0	0.0 – 9.6	12.2	.005**
15 days	8.5	1.3 – 33.8	0.0	0.0 – 13.7	8.5	.075
16 days	2.8	0.0 – 18.8	0.0	0.0 – 13.4	2.8	.094

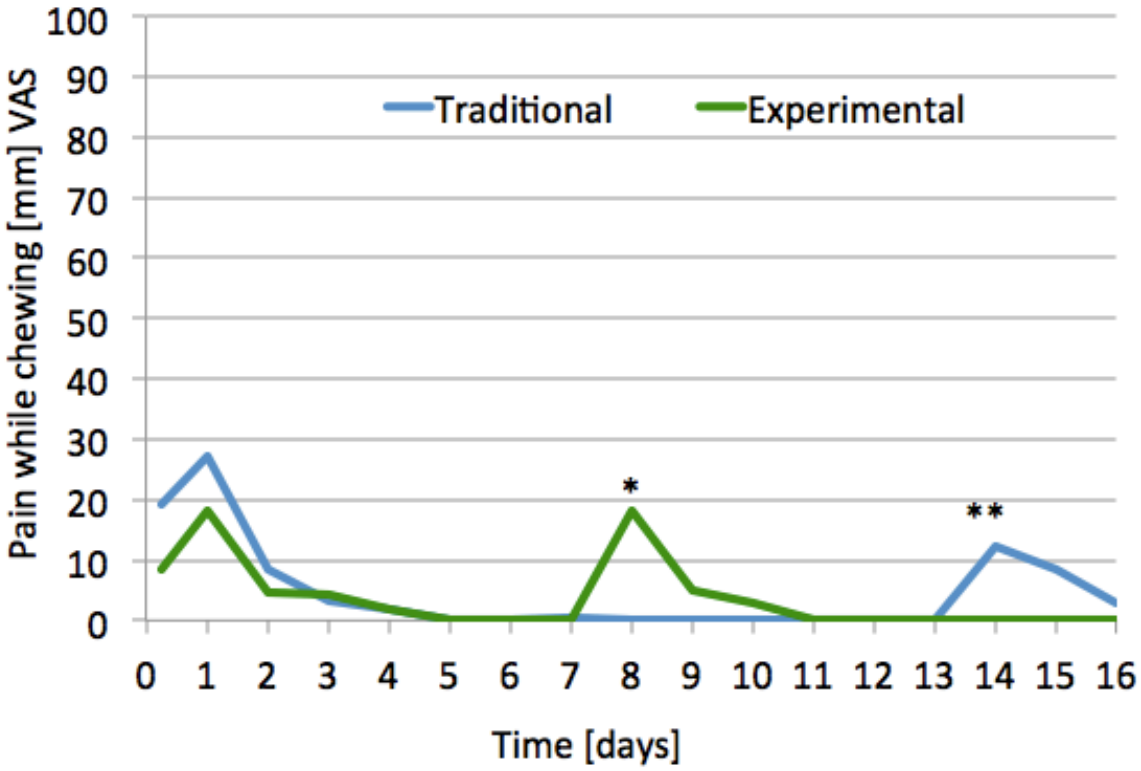

Figure 3.2. Pain, measured with a visual analogue scale (VAS), reported by Invisalign® patients when asked "My level of discomfort when chewing is:" [* indicate significant ($p<.05$) group differences, ** indicate significant ($p<.01$) group differences].

Eight days after initial insertion, patients in the experimental group reported significantly more discomfort than those in the traditional group. While the traditional group reported almost no pain, the experimental group reported pain that was approximately 75% as great as the pain they reported at 24 hours. At 14 days following insertion, after the traditional group had changed their aligners, they experienced significantly more pain than the experimental group, who had not changed their aligners. The pain that the traditional group reported at that time was approximately 98% as great as the pain that they reported at 24 hours. No significant differences were found in the

amount of pain reported by patients after they changed their respective aligners at 8 and 14 days. Reports of pain were highly variable among individuals.

The percent of patients who removed their aligners due to discomfort were consistently higher for the experimental than traditional group. However, the only statistically significant group differences occurred at 6 hours and at 9 days (Table 3.3, Figure 3.3). At 6 hours, 43.8% of the experimental group had removed their aligners compared to 9.1% of the traditional group. At day 9, 18.8% of the experimental group removed their aligners, while none of the patients in the traditional group removed their aligners. This was 2 days following an aligner change.

Table 3.3 Percentage of patients who removed their aligners due to discomfort, with Chi square test comparing group differences. [* indicate significant ($p<.05$) group differences].

Time	Traditional	Experimental	Chi Square Significance
6 hours	9.1	43.8	.013*
1 day	9.1	12.5	.735
2 days	4.8	25	.074
3 days	9.1	12.5	.735
7 days	4.5	0.0	.387
8 days	4.5	18.8	.159
9 days	0	18.8	.034*
14 days	4.5	6.3	.349
15 days	9.1	6.3	.477
16 days	9.1	6.3	.477

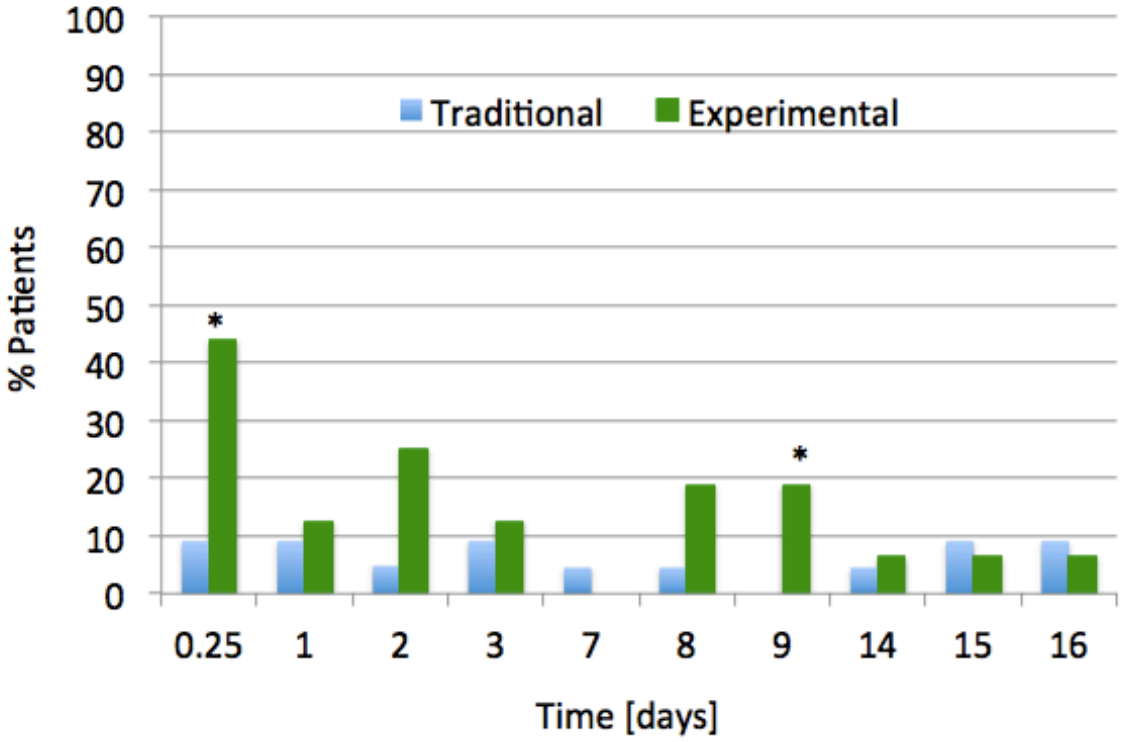

Figure 3.3. Percentage of patients who removed Aligners due to tooth related discomfort. [* indicate significant ($p<.05$) group differences].

The only significant difference in percentages of patients consuming analgesic medications because of tooth discomfort occurred on day 8, the day following the experimental group's aligner change (Table 3.4, Figure 3.4), when 18.8% of the patients reported consumption of analgesics. No significant differences were found between the groups in terms of patients consuming analgesics reasons other than tooth discomfort (Table 3.5, Figure 3.5).

Table 3.4. Percentage of patients who consumed analgesics due to tooth-related discomfort, with Chi square test comparing group differences. [* indicate significant (p<.05) group differences].

Time	Traditional	Experimental	Chi Square Significance
6 hours	13.6	37.5	.093
1 day	31.8	31.3	.97
2 days	9.5	18.8	.416
3 days	4.5	6.3	.816
7 days	0.0	6.3	.235
8 days	0.0	18.8	.034*
9 days	0.0	6.3	.235
14 days	13.6	0.0	.164
15 days	18.2	6.3	.299
16 days	9.1	6.3	.477

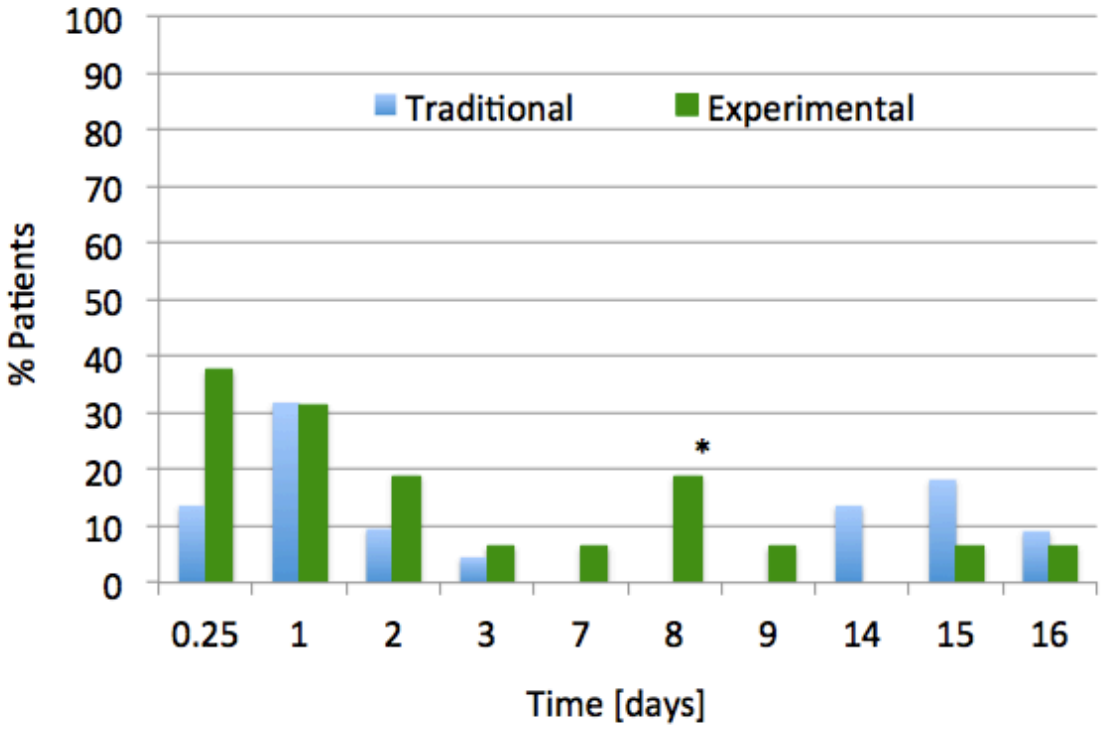

Figure 3.4. Percentage of patients consuming analgesics due to tooth related discomfort [* indicate significant (p<.05) group differences, ** indicate significant (p<.01) group differences].

Table 3.5 . Percentage of patients who consumed analgesics for a reason unrelated to tooth discomfort, with Chi square test comparing group differences.

Time	Traditional	Experimental	Chi Square Significance
6 hours	4.5	6.3	.816
1 day	4.5	6.3	.816
2 days	4.8	6.3	.843
3 days	4.5	6.3	.816
7 days	0.0	6.3	.235
8 days	4.5	6.3	.816
9 days	4.5	6.3	.816
14 days	4.5	12.5	.312
15 days	4.5	18.8	.166
16 days	4.5	18.8	.166

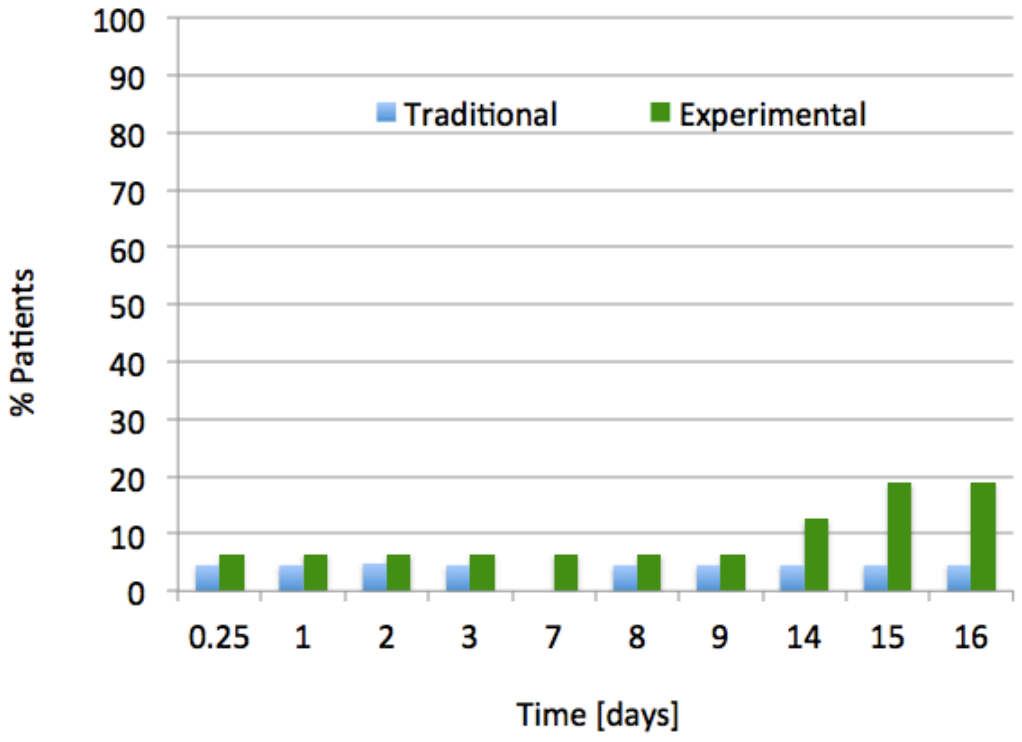

Figure 3.5. Percentage of patients taking analgesics for an issue unrelated to tooth discomfort

Discussion

Invisalign appliances produce patterns of pain during the first 7 days previously reported for other appliances. Pain increased approximately 6 hours following insertion of an orthodontic appliance, peaked at approximately 24 hours and returned to baseline after 5-6 days, which corresponds well with patterns previously reported. [24,25,30,31,32,33] Although the appliance is removable, patients are instructed to wear it for a minimum of 20 hours per day and the results are similar to previous studies of fixed appliances.

Peak pain produced 24 hours after insertion of the Invisalign appliances is less than produced with fixed appliances. The results showed a median pain scores at rest of 16.6% and 18.8% for the experimental and traditional aligner groups, respectively. Previous pain studies evaluating other modes of treatment, mostly fixed appliances, typically show a mean pain scores ranging between 40-50% at 24 hours. [24,30,31,25] This supports the work of Miller et al., who reported a significant difference in mean pain intensity between Invisalign and fixed appliances.[24] The relative pain reported in the present study was consistently less than pain previously reported for fixed appliances and archwires.[25,26,34]

Importantly, the lower pain scores reported in the present study may have been partially due to statistics that were used. Medians and interquartile ranges were reported rather than means due to the skewness and kurtosis of the data. It is well established that skewed data can bias both means and standard deviations. Because the VAS allows up to 100 and the sample sizes were small, a few individuals with low pain thresholds and tolerances could dramatically affect the mean. The means and standard deviations

reported by Miller et al. and Jones and Chan might also have been biased; subtracting one standard deviation from their means results in a negative values, which are not possible.[24,26]

Although their medians were likely lower than their reported means, this fails to completely explain why the scores overall lower scores reported in the current study. The current study suggests that most patients experience only a mild amount of pain from orthodontic treatment with Invisalign. Mastication with bite wafers provided a reduction in pain similar to that achieved with NSAIDs.[35] Sergl et al. found that fixed appliances produced a higher intensity of discomfort, pressure, tension, and sensitivity to teeth than removable appliances.[36] The differences in discomfort could have been due to the fact that Invisalign patients remove their appliances to eat and brush their teeth. The temporary cessation of pressure in the PDL may allow for changes in blood flow that provide some relief from the pain.

Force levels may not be a primary factor explaining the discomfort experienced by patients during initial orthodontic tooth movement. The current study failed to find a significant difference in pain reported by Invisalign patients by reducing the forces placed on teeth during the first seven days, despite the fact that the teeth in the experimental group had less force placed upon them. Boester and Johnston were the first to challenge the notion that lighter forces are more comfortable; their paper was important because it actually measured the pain experience of the patient rather than evaluating examining histology.[15] They found no significant differences in pain between different force levels, as did a number of other investigators evaluating the effects of forces, archwire deflection, archwire sizes, and initial malalignment.[16,17,26] As such, the

assumption that low constant forces are the ideal for moving teeth with a minimum amount of pain deserves reconsideration.

Difference in hyalinization related to the amount of force applied may, therefore, not be indication of the pain that patients perceive. Reitan was among the first to show histologic differences in semi-hyalinization on the pressure side.[14] The key assumption was that this greater level of aseptic necrosis would produce a more painful experience for the patient. More recently, Bohl et al. showed in beagle dogs that hyalinization occurs in the presence of forces as light as 25 g and as heavy as 300 g.[37] Although larger areas of hyalinization were seen in response to heavier force levels, they concluded that while hyalinization limits tooth movement, this limitation is not force dependent as the rate of tooth movement was not affected. Even with light forces, focal points of hyalinization form which limit tooth movement similar to larger areas; the amount of hyalinization does not affect velocity.[38] The linchpin is that the widely taught notion that lighter forces cause less pain, which has been based on the testimony of experts and animal studies drawing conclusions about pain levels from histological specimens may be inaccurate.[11,14,39] The research that has measured pain levels directly in patients does not support such a view. Assuming that 1) heavier forces create more hyalinization and 2) that heavier forces do not induce more pain, then the assumption that the amount of hyalinization is the prima facie cause of pain must be rejected.

Furthermore, there were no significant differences found between the groups when comparing the amount of pain reported following their first aligner changes. If heavy forces cause greater amounts of discomfort, then the traditional group should have reported significantly higher median pain scores following their aligner change, but this

was not the case. Altered force levels with the Invisalign appliance and the effect upon discomfort has not previously been studied. The purpose of the investigation was to consider whether the lighter pressures placed on the teeth upon insertion would mean a more comfortable experience for the patient during orthodontic tooth movement. The results of the current study suggest that force levels within the range studied are unimportant as they relate to discomfort.

When they initially inserted and when they changed their aligners, patients reported significant increases in discomfort. Although the median pain intensity scores were low, a significant increase in pain above baseline was established at initial insertion and at each aligner change. This has not been previously reported. This supports the idea that placing force on teeth results in measurable pain. Because the experimental protocol calls for twice the number of aligner changes, it is possible that it would cause twice as many significant pain events. In other words, increasing the number of aligners is not advisable.

Patients in the experimental group reported removing their aligners significantly more due to discomfort. While they were statistically significant only at 6 hours and 9 days, the group differences were consistent. The lack of differences at the other time points may have been due to small sample sizes. These results suggest that trays that place less pressure on teeth cause significantly more discomfort. Lighter forces causing significantly more pain has not previously been reported in the literature or discussed in orthodontic texts.

The major limitation of the study was the small sample size. Because there was large individual variation in pain threshold and tolerances, individuals vary widely along

the VAS. Large ranges of variation have been reported in previous studies.[26,34] This becomes problematic when attempting to determine differences between groups. In the current study, medians and interquartile ranges were reported to control the effect that a few outliers may have had on the means.

Conclusions

It has long been suggested that there is point along the force spectrum at which maximal tooth movement and minimal discomfort can be achieved. Neither this study nor the literature support such a notion. Forces sufficient to move teeth produce compression and tension in the periodontal ligament, which initiate an inflammatory cascade to remove damaged tissue, orchestrate repair, and sensitize pain receptors. Reducing forces does not affect discomfort reported by patients. Patients experience discomfort that does not follow a dose-response relationship with the amount of force applied to teeth. If the goal is to reduce the amount of discomfort experienced by patients, future research should be directed toward techniques to best manage orthodontic pain, which appears to be inevitable and independent of force magnitude.

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