

Orthodontic pain: from causes to management—a review

Vinod Krishnan

Department of Orthodontics, Rajas Dental College, Tirunelveli District, Tamilnadu, India

SUMMARY Orthodontic pain, the most cited negative effect arising from orthodontic force application, is a major concern for parents, patients, and clinicians. Studies have reported this reaction to be a major deterrent to orthodontic treatment and an important reason for discontinuing treatment. Surprisingly this area, which requires attention in clinical practice as well as in research, is ignored as evidenced by the scarcity of publications on the topic in comparison with other areas of orthodontic research. This review attempts to organize the existing published literature regarding pain, which appears as part of orthodontic mechanotherapy and to address questions that might arise in a clinical setting from the viewpoint of clinicians and patients/parents. It also provides an overview of current management strategies employed for alleviating orthodontic pain.

Introduction

Pain, which includes sensations evoked by, and reactions to, noxious stimuli, is a complex experience and often accompanies orthodontic appointments. This, among the most cited negative effects of orthodontic treatment, is of major concern to patients as well as clinicians (Oliver and Knapman, 1985; Kluemper *et al.*, 2002) and is evident in recent publications (Asham and Southard, 2004; Keim, 2004). Surveys performed to determine the experience of orthodontic pain have rated it as a key deterrent to orthodontic therapy and a major reason for discontinuing treatment (Haynes, 1974; Oliver and Knapman, 1985; Brown and Moerenhout, 1991; Kluemper *et al.*, 2002). One survey rated pain as the greatest dislike during treatment and fourth among major fears and apprehensions prior to orthodontic treatment (O'Connor, 2000).

Pain is a subjective response, which shows large individual variations. It is dependent upon factors such as age, gender, individual pain threshold, the magnitude of the force applied, present emotional state and stress, cultural differences, and previous pain experiences (Ngan *et al.*, 1989; Brown and Moerenhout, 1991; Scheurer *et al.*, 1996; Firestone *et al.*, 1999; Bergius *et al.*, 2000). Surveys regarding the percentage of patients experiencing pain have reported values ranging from 70 (Caucasian population) to 95 (Asian population) per cent (Oliver and Knapman, 1985; Kvam *et al.*, 1989; Lew, 1993; Scheurer *et al.*, 1996; Firestone *et al.*, 1999). One report has even stated that 8 per cent of a study population discontinued treatment because of pain (Patel, 1989). Surprisingly, this important area, in clinical practice as well as research, is ignored, as evidenced by the scarcity of publications. This review is an attempt to organize the existing literature regarding pain, which appears as part of orthodontic mechanotherapy, and attempts to address questions that might arise in a clinical setting from the viewpoint of clinicians and patients/parents. It also

provides an overview of current management strategies employed for alleviating orthodontic pain.

Orthodontic causes of pain—what are they?

It is clear from the existing literature that all orthodontic procedures such as separator placement, archwire placement and activations, application of orthopaedic forces and debonding produce pain in patients. It is also clear that fixed appliances produce more pain than removable or functional appliances and there exists little correlation between applied force magnitude and pain experienced.

The various discomforts experienced by patients after appliance placement are often described by them as feelings of pressure, tension, soreness of the teeth, and pain as such (Ngan *et al.*, 1989). Clinicians usually respond to the most frequently asked question 'Will it hurt?' with the answer 'There may be some discomfort associated with all orthodontic procedures such as placement of separators, archwire placement and activations, elastic wear and debonding'. The two most important parts of orthodontic pain—its duration and intensity are often ignored. It is known that the above-mentioned procedures will cause pain but what is not known is 'why they cause pain?' It is reported that orthodontic procedures will reduce the proprioceptive and discriminating abilities of the patients for up to 4 days, which result in lowering of the pain threshold and disruption of normal mechanisms associated with proprioception input from nerve endings in the periodontal ligament (PDL; Soltis *et al.*, 1971). At the same time, there will be pressure, ischaemia, inflammation, and oedema in the PDL space (Furstman and Bernick, 1972).

Burstone (1962) reported an immediate and delayed painful response after orthodontic force application. He attributed the initial response to compression and the delayed response to hyperalgaesia of the PDL. This

hyperalgesia has been related to prostaglandins (PGEs), which make the PDL sensitive to released algogens such as histamine, bradykinin, PGEs, serotonin, and substance P (Ferreira *et al.*, 1978; Polat *et al.*, 2005). It is clear that all orthodontic procedures will create tension and compression zones in the PDL space resulting in a painful experience for the patients.

Orthodontic separation and pain

Creating space mesially and distally to teeth, which are to be banded, forms the initial step in fixed orthodontic mechanotherapy. It is well-known that placement of orthodontic separators (brass wire, elastomerics, spring type steel separators, and latex elastics) results in a painful experience for almost all patients (Ngan *et al.*, 1989, 1994; Bondemark *et al.*, 2004). Two controlled clinical trials performed by Ngan *et al.* (1989, 1994) concluded that there was discomfort associated with separator placement, which usually starts within 4 hours of insertion. The level of discomfort increases over the next 24 hours and decreases to pre-placement level within 7 days. A recent report (Bondemark *et al.*, 2004) has also addressed this issue. They evaluated and compared the separation effect and patient perception of pain and discomfort to two types of orthodontic separators (elastomeric and spring type) but found no statistically significant difference between the discomfort caused by the two types of separators. They reported that the worst pain was experienced at day 2 and subsided almost completely by day 5.

An electromyographic (EMG) study (Michelotti *et al.*, 1999), performed to evaluate the motor and sensory changes associated with separator placement, showed a decrease in motor output as well as pressure pain threshold in muscles of mastication. They suggested this to be a protective mechanism against further damage to the injured part of the masticatory system. It is clear that pain is associated with the process of orthodontic separation and starts within 4 hours of its placement with a peak level at day 2 that might last for 7 days.

Archwire placement and activation

Pain associated with initial archwire placement has been previously researched. Jones (1984) reported that pain is experienced by the majority of patients 4 hours after archwire placement, which will peak at 24 hours and then decline. Various authors, who performed the same research in other racial and ethnic groups, confirmed these findings (Ngan *et al.*, 1989, 1994; Scheurer *et al.*, 1996; Firestone *et al.*, 1999; Erdinç and Dinçer, 2004; Polat *et al.*, 2005). Jones and Chan (1992b) stated that pain from archwire placement can be worse in some patients and could even be more than that experienced after tooth extraction. They observed a diurnal variation in pain experienced by patients—with evening and nights showing the highest

scores. The pain will usually last for 2–3 days and will gradually decrease in its intensity by fifth or sixth day (Jones and Chan, 1992a, b).

Comparing various archwires to determine differences in pain perception showed no statistically significant results. No difference in the intensity, prevalence, or duration of pain between different archwires was found (Jones and Richmond, 1985; Fernandes *et al.*, 1998; Erdinç and Dinçer, 2004). Erdinç and Dinçer (2004), in agreement with others (Ngan *et al.*, 1989, 1994; Scheurer *et al.*, 1996), found that patients reported more pain experience in anterior than in posterior teeth because of the differences in root surface area, increased involvement of anterior teeth during levelling, and greater use of anterior teeth for biting. Fernandes *et al.* (1998) reported that after 11 hours of force application, a higher pain perception was experienced in the lower than in the upper arch.

A literature search regarding pain perception following archwire activation resulted in few publications. Gianelly and Goldman (1971) stated that the conditioned and/or nociceptive reflexes elicited as a result of orthodontic archwire activation often leads to avoidance of chewing hard foods by the patients. Smith *et al.* (1984) and Goldreich *et al.* (1994), through different experiments, evaluated the effect of orthodontic archwire activation on the masseter muscle through EMG activity. They observed a reduction in masseter muscle activity and attributed this to the noxious stimuli emulating from the periodontal membrane or paradental receptors triggering a reflex mechanism, which caused inhibition of jaw-closing muscles (EMG activity during induced pain has been shown to increase when jaw-closing muscles act as antagonists, Lund *et al.*, 1983). In brief, both archwire placement as well as activation will cause pain and might affect dietary habits as well as the daily life activities of patients.

Appliance type

The effect of different appliances (fixed and removable) on pain experience has been evaluated. Oliver and Knapmann (1985) found no difference in the level of discomfort produced by fixed or removable appliances. Sergl *et al.* (1998) contradicted this finding and stated that fixed and functional appliances produced a higher intensity of discomfort than removable appliances. Patients wearing fixed appliances reported higher values for intensities of pressure, tension, pain, and sensitivity to teeth. Their findings were in agreement with Stewart *et al.* (1997) that fixed appliances create more pain when compared with removable appliances.

Initial tooth positions and force levels

The concept of light forces producing more physiological and less painful tooth movement is a matter of debate. Hixon *et al.* (1969), who favoured application of heavier

forces for canine retraction, stated that higher forces per unit area increased the rate of biological response. Gianelly and Goldman (1971) argued that large forces caused greater periodontal compression and thus more pain. They stated that some pain accompanies every orthodontic appointment. Jones and Richmond (1985) evaluated the relationship between initial tooth positions, applied force levels, and experienced pain but observed no statistically significant correlation among the three parameters. Those authors suggested that the degree of displacement of the tooth from the archwire to indicate the level of applied force and thereby discomfort experienced by the patient should not be considered. All these assumptions and findings point to the fact that malocclusions, however severe, when undergoing orthodontic treatment will elicit a painful response, and little correlation exists between the degree of pain response and applied force magnitude.

Orthopaedic forces and sutural strain

Craniofacial orthopaedics utilizes mechanical forces of a high magnitude, which when applied are absorbed and transmitted to the craniofacial complex. These forces will produce a series of reactions characterized by tissue displacement, deformation, and development of internal stress (Mao, 2002; Mao *et al.*, 2003). Ten Cate *et al.* (1977), after exerting a sagittal expansion force in rats, observed traumatic tears, exudates, death of fibroblasts, disruption of collagen fibres, and acute inflammation. As part of the inflammatory process, the patient perceives a painful sensation, which is often expressed in the whole craniofacial region. There are reports in the literature that demonstrate painful experiences after application of expansive force with rapid palatal expanders (Handelman, 1997; Needleman *et al.*, 2000; Schuster *et al.*, 2005). Needleman *et al.* (2000) concluded that vast majority of children undergoing rapid palatal expansion experience pain, which occurs during the initial phase and diminishes thereafter. Egolf *et al.* (1990) found that approximately 28 per cent of patients reported pain as the factor which prevented them from wearing headgear or elastics.

Patients often experience discomfort after 24 hours of headgear wear and there is a sharp decline in pain after 3 days (Cureton, 1994; Ngan *et al.*, 1997). Cureton (1994) evaluated the discomfort levels associated with combination therapy, headgear, and a transpalatal arch (TPA). They suggested that wearing of a headgear and a TPA should never be started together and that headgear wear should precede TPA wear by at least 1 week. Ngan *et al.* (1997), who evaluated levels of masticatory muscle pain and EMG activity in patients treated with protraction headgear, concluded that protraction headgear does not induce muscle pain or produce an increase in muscle activity. It is clear that the pain associated with orthopaedic devices is not of a

muscular nature but a part of the acute inflammatory reaction occurring at the sutural regions.

Debonding

Williams and Bishara (1992) evaluated the threshold level for patient discomfort at debonding and concluded that tooth mobility and force application were the two important influencing factors. They found intrusive forces to produce less pain at debonding in comparison with forces applied in a mesial, distal, facial, lingual, or extrusive direction. They suggested applying finger pressure or asking the patient to bite on a piece of cotton roll to minimize pain while debonding. Rinchuse (1994), in another report, described the use of an occlusal rim wax for pain-free debonding. Apart from these two studies, there appear to be no other literature reports, which assessed discomfort levels during debonding.

What is the underlying mechanism for orthodontic pain?

There is no doubt that the perception of orthodontic pain is part of an inflammatory reaction causing changes in blood flow following orthodontic force application. This is known to result in the release of various chemical mediators eliciting a hyperalgaesia response. Recent research has started revealing the molecular basis of orthodontic pain with demonstration of the presence as well as elevation in levels of various neuropeptides released. Even though there are a number of publications, there appears to be some missing links in the pathway of pain arising as part of orthodontic mechanotherapy, clarification of which requires further research.

Orthodontic tooth movement is known to cause inflammatory reactions in the periodontium and dental pulp, which will stimulate release of various biochemical mediators causing the sensation of pain. The perception of orthodontic pain is due to changes in blood flow caused by the appliances and has been correlated with the release and presence of various substances, such as substance P, histamine, enkephalin, dopamine, serotonin, glycine, glutamate gamma-amino butyric acid, PGEs, leukotriens, and cytokines. The literature regarding the increase in the levels of these mediators, which elicit hyperalgaesia response following force application, is replete in orthodontics (Yamasaki *et al.*, 1984; Walker *et al.*, 1987; Davidovitch *et al.*, 1988; Nicolay *et al.*, 1990; Davidovitch, 1991; Saito *et al.*, 1991b; Grieve *et al.*, 1994; Alhashimi *et al.*, 2001).

Processing of complex information arising from mechanical force application induces recruitment of neurons, which act by the way of chemical mediators as modulators of the effector response to the stimulus (Vandevska-Radunovic, 1999). Apart from the classic constituents mentioned above, peripheral nerve fibres also

participate in the inflammatory process associated with tooth movement (neurogenic inflammation). This involves release of neuropeptides after antidromic stimulation of afferent nerve endings and initiation of an inflammatory reaction. These neuropeptides released are known to elicit a painful response (Vandevska-Radunovic, 1999). Kato *et al.* (1996) examined the distribution of nerve fibres containing neurofilament protein (NFP), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and neuropeptides Y (NPY) in the PDL of the rat first molar after mechanical force application. They observed an increase in number of NFP and CGRP containing nerve fibres at both the stretched and the compressed sides after 3 days of force application, which returned to normal after 14 days. They concluded that NFP-, CGRP-, VIP-, and NPY-containing nerve fibres play an important role in blood flow regulation, tissue remodelling, and modulation of pain perception during tooth movement. This finding was in concordance with earlier reports (Kvinnslund *et al.*, 1989; Kvinnslund and Kvinnslund, 1990; Saito *et al.*, 1991a). Norevall *et al.* (1995) also agreed on the role of CGRP and substance P on tooth movement, but contradicted the role of other neuropeptides such as VIP and NPY.

Substance P, the sensory neuropeptides released by sensory peripheral nerve endings, is known to modify the secretion of other proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α from monocytes (Nicolay *et al.*, 1990; Norevall *et al.*, 1995; Alhashimi *et al.*, 2001). CGRP, another major sensory neuropeptide, is also known to evoke the release of IL-6, IL-8, and TNF- α from different cell lines (Norevall *et al.*, 1995). Yamaguchi *et al.* (2004) found a significant increase in the release of three major cytokines (IL-6, IL-8, and TNF- α) by human dental pulp cells after 12 hours of mechanical force application. They concluded that the major neuropeptides, as well as the proinflammatory cytokines, might be involved in pulpal inflammation during orthodontic tooth movement. Deguchi *et al.* (2003) demonstrated the presence of galanin (GAL)-immunoreactive nerve fibres in the PDL during experimental tooth movement. GAL fibres have been proposed to act as an endogenous antinociceptive modulator of spinal cord excitability. They have suggested increased expression of GAL-immunoreactive fibres to represent upregulation of GAL (as part of the body's natural defence to reduce pain) for antinociceptive effect in spinal cord.

The correlation between brain cell activation and clinical sensation of pain and discomfort during orthodontic tooth movement is a matter of interest. The expression and distribution of *c-Fos* or the like neurons in the trigeminal sensory nuclear complex, parabrachial nucleus, and paraventricular nucleus of hypothalamus and thalamus, have been demonstrated (Kato *et al.*, 1996; Yamashiro *et al.*, 1998, 2001; Aihara *et al.*, 1999; Fujiyoshi *et al.*, 2000; Hiroshima *et al.*, 2001). It is clear from these studies that trigeminal nucleus caudalis forms important relay nuclei for

processing orofacial sensory information and an increased expression of *c-Fos* can be found in this nucleus after orthodontic force application. On further evaluation, it was observed that the labelled neurons for *c-Fos* were mainly located in the superficial laminae (lamina I and II) at the dorsomedial and ventral edges, predominantly near the apex and also in the transitional zone to the interpolaris. This superficial lamina is known to contain nociceptive-specific neurons (Bester *et al.*, 1997; Jasmin *et al.*, 1997). This was confirmed by the findings of a reduction in the expression of these neurons in patients where pre-treatment morphine was administered (Aihara *et al.*, 1999). Furthermore, employing naloxone, a morphine antagonist, reversed this effect (Hiroshima *et al.*, 2001).

Apart from spinal trigeminal caudalis, expression patterns of *c-Fos* in dorsal raphe nucleus, which is considered important as far as pain modulation is concerned, have been found. This dorsal raphe nucleus, together with PAG and LC, is known to play a major role in central nociceptive circuits (Magdalena *et al.*, 2004). It is reported that some of these fibres have serotonin as the mediator and this correlates with the finding that experimental tooth movement activates the bulbospinal serotonergic pathway (Yamashiro *et al.*, 2001). This rapidly advancing field in pain research, utilizing orthodontic tooth movement as a model, provides insights into the intricate mechanisms of neuronal involvement. However, there are a number of missing links in the pathway of pain arising as part of mechanical procedures during orthodontic mechanotherapy.

Are there any factors that influence a painful response to orthodontic force?

There exists a non-linear relationship between age, gender, psychological state and cultural background in pain perception following placement of an orthodontic appliance. The relationship between the psychological well being of patients and orthodontic pain perception is proven beyond doubt. It is clear from the published literature that females express more pain than males, and adolescents report higher levels of pain than pre-adolescents and adults.

It is well-known that an individual's 'physiological and psychological susceptibility' can become a significant factor in the intensity of tissue discomfort caused by the physical effects of appliances. It has been reported that the pain experienced by patients does not seem to be directly related to the magnitude of force exerted but relies heavily on the psychological well-being of the individual (Dubner, 1968; Brown and Moerenhout, 1991; Serl *et al.*, 1998; Bergius *et al.*, 2000). Factors such as perceived severity of malocclusion and personal control orientation [a locus of control orientation is a belief about whether the outcomes of our actions are contingent on what we do (internal/personal control orientation) or on events outside our personal

control (external control) orientation <http://www.wilderdom.com/psychology/loc/LocusOfControlWhatIs.html>] affect or rather determine behaviour during orthodontic treatment (Rotter, 1966). Serfl *et al.* (1998) confirmed these findings and reported a very distinct correlation between a patient's attitude towards treatment and discomfort felt after appliance insertion.

Traditionally, it is believed that females are 'fragile' and sensitive to pain, while males are more stoical and can tolerate more pain (Bergius *et al.*, 2000). Conflicting results have, however, been reported with some showing that males are more willing to tolerate pain than females, but others that there is no differences between males and females in reporting the feeling of pain with respect to threshold (Ingersoll, 1982). A literature search revealed only two reports, which addressed this issue (Ngan *et al.*, 1989; Erdinç and Dinçer, 2004), who both found that girls reported more discomfort/pain and ulcerations than boys, during fixed appliance treatment.

The 'effect of age' on pain perception is difficult to compare as far as orthodontic treatment is concerned. This is mainly because of the different treatment approaches followed for patients of different ages. However, studies reporting this issue reveal conflicting results. Most favour the opinion that adult subjects perceive more pain than young patients (Jones and Richmond, 1985; Brown and Moerenhout, 1991; Jones and Chan, 1992a, b; Scheurer *et al.*, 1996; Fernandes *et al.*, 1998). In a study utilizing a visual analogue scale (VAS), Ngan *et al.* (1989) found no statistically significant difference in pain perception between adolescents and adults. An extensive report by Brown and Moerenhout (1991), comparing pain perception with a pain rating index in pre-adolescents, adolescents, and adults, found that adolescents reported a higher level of pain than pre-adolescents and adults. This phenomenon was noted after all phases of treatment such as separator placement, banding, archwire placement, and activations. They rationalized this phenomenon by a statement that 'reported pain could be somatization of either anxiety or depression'. This might help the patient to translate feelings of anxiety or depression into a tangible psychological problem.

There is strong evidence that some experiences of pain are universal, while others are 'culture' specific. Some ethnic groups encourage social attitude and behaviour and persons in these groups are often expected to openly express his/her responses. These patterns are learned and transmitted largely in families (Bergius *et al.*, 2000). Thus, the family as well as surroundings should be considered as an important source of early learning with no exception with respect to pain perception and its response.

It can be stated that there exists a non-linear relationship between age, gender, psychological state, and cultural background in pain perception following placement of orthodontic appliances and these factors should be considered before beginning treatment.

How to evaluate pain?

There is a well-defined classification system for orthodontic pain proposed by Burststone (1962). It appears to be valid even now and to have stood the test of time. In order to study or evaluate pain, patient interview/questionnaire and ratings with VAS, McGill pain questionnaire (MPQ), Verbal Rating Scales (VRS) and algometers can be effectively used.

Classifying pain

Burststone (1962) classified a painful response to orthodontic mechanics in two ways: one depends on the relationship of force application with pain and the other according to the time of onset. According to that author, the degree of pain perceived in response to the amount of force application can be divided into three:

1. First degree: the patient is not aware of pain unless the orthodontist manipulates the teeth to be moved by the appliance, e.g. using instruments such as a band pusher or force gauge.
2. Second degree: pain or discomfort caused during clenching or heavy biting—usually occurs within the first week of appliance placement. The patient will be able to masticate a normal diet with this type of pain.
3. Third degree: if this type of pain appears, the patient might be unable to masticate food of normal consistency.

Based on time of onset, Burststone (1962) further classified pain as follows:

1. Immediate: which is associated with sudden placement of heavy forces on the tooth, e.g. hard figure of eight tie between the central incisors to close a midline diastema.
2. Delayed: produced by variety of force values from light to heavy and representing hyperalgesia of the periodontal membrane. This type of pain response decreases with time i.e. the pain reaction might start as third degree but become second or a first degree with the passage of time.

Studying pain

It is well-known that correct measurement of pain is an essential part of its evaluation, and adaptation of methods to control it. Various approaches have been used to measure and evaluate pain perception in orthodontic patients. The methods adopted vary from traditional surveys with pre-tested questionnaires, rating with VAS (Linacre, 1998), MPQ (Melzack, 1975), VRS (Jones and Chan, 1992a, b), and algometers (Simmons, 1994). Most of the studies have utilized a VAS, which is designed to present the respondent with a rating scale with minimum constraints (Linacre, 1998). The respondent is expected to mark a location on the

line corresponding to the amount of experienced pain. This has been claimed to have two advantages:

1. It provides freedom to choose the exact intensity of pain.
2. It gives maximum opportunity for expression in an individual personal response style.

Another common method used in medical research, but less explored in orthodontics, is the MPQ (Melzack, 1975). This consists of three major classes of word descriptors—sensory, affective, and evaluative—that are used by patients to specify subjective pain experience. It also contains an intensity scale and other items to determine the properties of pain experience. The main advantage of the MPQ is the provision to identify quantitative measures of clinical pain. The pain rating index is a short form of MPQ, which can be used in routine clinical practice because of its user-friendly nature.

VRS is another method to evaluate orthodontic pain (Jones and Richmond, 1985; Jones and Chan, 1992a, b). This consists of a list of adjectives to describe different intensities of pain. The method requires patients to read a list of adjectives and select the word or phrase that best describes their level of pain. An adequate VRS scale should include adjectives that reflect extremes such as 'no pain' and 'excruciating/extremely intense pain'.

Simmons (1994) proposed use of an algometer to evaluate pain in patients sitting in dental chair. A data acquisition system was utilized to record the measurement of forces applied to teeth as fixed orthodontic appliances were adjusted. The device contains two input systems—one is a metal strip attached to the orthodontic brackets and the other, a 5V signal from a remote control television unit that the patient activates when they begin to feel pain. More research is needed in this electronic system of pain assessment before clinical application, so that accurate and reliable results other than subjective evaluation from patients can be obtained.

Does orthodontic pain have any effect on patient compliance and daily activities?

The literature supports the fact that orthodontic pain has a definite influence on compliance and daily activities of patients. The major reasons affecting patient compliance are the functional and aesthetic impairment produced by the appliance. Almost all patients undergoing orthodontic treatment have moderate to extreme difficulty in chewing and biting foods of firm to hard consistency, which causes them to change the consistency of their food.

Patient compliance

The literature is replete with data confirming that the discomfort from orthodontic appliances can be a significant factor affecting patient compliance (Patel, 1989; Brown and

Moerenhout, 1991; Sergl *et al.*, 1998; O'Connor, 2000). The primary causes for poor co-operation have been attributed to pain, functional, and aesthetic impairment caused by the appliances. This has even resulted in a discontinuation of treatment or its early termination (Patel, 1989). Sergl *et al.* (1998) confirmed these findings and reported a significant correlation between patient co-operation and complaints during the 6-month period after appliance placement. Many patients as well as parents consider initial lack of information about possible discomfort during treatment to be a major cause of the poor compliance exhibited. The literature suggests that the patients' initial attitude towards orthodontics should be understood during the diagnostic phase itself and should be discussed with the patients in all its reality. This procedure, termed as 'rational restructuring' in psychology (Todesco *et al.*, 1992) will prepare the patients to encounter discomfort during treatment through their own methods and also with the help of a specialist.

Daily activities

Brown and Moerenhout (1991) reported that pain from orthodontic treatment has a definite influence on daily activities of patients. The pain appearing within the first 48 hours is considered to be so disturbing that it causes wakeful nights and consumption of medication. Almost all patients from various studies reported moderate to extreme difficulty in chewing and biting foods of a firm to hard consistency, which caused them to change the consistency of their diet (Brown and Moerenhout, 1991; Bergius *et al.*, 2000). Erdinc and Dinger (2004) evaluated this problem but observed no statistically significant results. Even though the results were statistically insignificant, they reported that approximately 50 per cent of their patients had problems with their daily activities at 6 hours and on days 1 and 2. There was a decrease in the severity of discomfort and the number of patients experiencing it from day 3 onwards.

How can orthodontic pain be managed?

The existing literature supports the use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain control, even though other methods (such as anaesthetic gel, bite wafers, transcutaneous electrical nerve stimulation, low level laser use and vibratory stimulation) have been suggested. The major concern regarding NSAIDs is the interference produced on inflammation associated with tooth movement process. Low doses administered for one or two days in the initial stages will not affect the tooth movement process as such. The current trend is directed towards use of pre-emptive or pre-operative analgesics, which are administered at least one hour before every orthodontic procedure.

It is imperative that pain control during orthodontic treatment should be considered an important aspect of orthodontic mechanotherapy and NSAIDs remain the most

preferred method for pain control during orthodontics. Lack of an appropriate protocol for their administration after orthodontic appointments is considered to be a major drawback requiring attention in future research.

Simmons and Brandt (1992) were the first to recommend the use of acetaminophen for managing orthodontic pain, while Pagenelli (1993) favoured flurbiprofen. Efforts to compare various drugs in managing orthodontic pain were performed by Ngan *et al.* (1994). They compared ibuprofen, aspirin, and a placebo and concluded that ibuprofen was the most effective analgesic in orthodontic pain management. Numerous studies investigating various drugs such as ibuprofen, aspirin, acetaminophen, misoprostol, indomethacin, naproxan sodium, and recently introduced cox-2 inhibitor, rofecoxib (Chumbley and Tuncay, 1986; Kehoe *et al.*, 1996; Roche *et al.*, 1997; Steen Law *et al.*, 2000; Bernhardt *et al.*, 2001; Sari *et al.*, 2004; Polat and Karaman, 2005) have been published. All agreed upon the fact that these drugs effectively reduce the discomfort and pain caused by appliances by inhibiting or at least reducing the inflammatory response caused by the applied force.

It is clear that, release of PGE, the primary mediators of inflammatory response following force application, will be inhibited by NSAIDs causing a reduction in tooth movement (Walker and Buring, 2001). Kyrkanides *et al.* (2000) evaluated the molecular level mechanisms behind this process of inhibition. They reported an increase in the levels of MMP-9 and MMP-2 along with collagenase activity followed by reduction in procollagen synthesis after NSAID administration. The whole process is the result of inhibition of cyclooxygenase activity and results in altered vascular and extracellular collagen remodelling, effecting a reduction in the rate of tooth movement. A recent development in this area of pain management is the introduction of rofecoxib, the cox-2 inhibitor. It has been reported that this drug has no effect on PGE1 levels and can be safely used for pain control during orthodontic mechanotherapy (Sari *et al.*, 2004). However, in light of findings regarding safety on administration of cox-2 inhibitors (<http://www.rheumatology.org/publications/hotline/0402cox2.asp>), more studies need to be carried out before it is administered in routine clinical practice.

Pre-emptive or pre-operative analgesic administration to decrease post-operative pain has become the focus of recent research in orthodontics. Pre-emptive analgesia will block the afferent nerve impulses before they reach the central nervous system, abolishing the process of central sensitization (Woolf, 1991). Steen Law *et al.* (2000) demonstrated that pre-emptive ibuprofen administered at a dose of 400 mg 1 hour before separator placement results in a significant decrease in pain on chewing at 2 hours after the procedure. Bernhardt *et al.* (2001) and Polat *et al.* (2005) confirmed this finding. Polat *et al.* (2005) compared the effect of naproxan sodium (550 mg) and ibuprofen (400 mg) administered pre-operatively before archwire placement

and found naproxan sodium to be more effective than ibuprofen after 2 and 6 hours and even at night after archwire placement. They suggested that, in addition to the pre-operative dose, at least one or two post-operative doses should be administered for complete pain control after orthodontic appointments.

Apart from analgesics, other approaches have been tested to reduce pain from orthodontic procedures. Keim (2004) described an anaesthetic gel 'oraqix', which is a combination of lidocaine and prilocaine in 1:1 ratio by weight. The findings suggest that it may be useful when performing orthodontic procedures such as band placement and cementation, archwire ligation, and band/bracket removal. The advantage of this system is its delivery method, which simply introduces the gel into the gingival crevice. The procedure is reported to be entirely painless.

Chewing gum or a plastic wafer during first few hours of appliance activation in order to reduce pain has been suggested (Proffit, 2000). This will temporarily displace the teeth sufficiently to allow blood to flow through compressed areas preventing a build up of metabolic products. White (1984) found that approximately 63 per cent of patients reported less discomfort after chewing Aspergum—a weak analgesic chewing gum with aspirin, after orthodontic mechanotherapy. Hwang *et al.* (1994) evaluated the effect of therabite wafers in reducing pain. They observed relief of pain in the majority of patients (56 per cent) but the rest of the subjects reported increased discomfort after chewing wafers. The relationship between suppression of pain with chewing gum and serotonergic (5-HT) neurons implicated in nociceptive transmission has been reported by Mohri *et al.* (2005). According to those authors, the rhythmic behaviour of chewing suppresses nociceptive responses via the serotonergic (5-HT)-descending inhibitory pathway.

Anecdotal reports on other techniques found in the literature for management of orthodontic pain include vibratory stimulation (Marie *et al.*, 2003), transcutaneous electrical nerve stimulation (TENS; Roth and Thrash, 1986) and low-level laser application (Lim *et al.*, 1995). The use of vibratory stimulation to reduce orthodontic pain was first reported by Marie *et al.* (2003), but on detailed analysis, it was found that most of the patients were not able to tolerate the vibrations, once the discomfort sets in. This led to the recommendation that, if employed, it should be used prior to the onset of pain (Marie *et al.*, 2003). Roth and Thrash (1986) evaluated the effect of TENS in reducing periodontal pain after separator placement. Although it was effective in reducing pain within 6 seconds of electrode placement, and the technique was used by others, no additional reports have been published. Lim *et al.* (1995) in a clinical investigation on the efficacy of low-level laser therapy in reducing orthodontic pain found discouraging results and it was not found to produce immediate pain relief in orthodontic patients.

The overall findings indicate that analgesics are still the main treatment modality to reduce orthodontic pain. Recent research towards its pre-emptive use as well as concentration on those agents not involving PGE synthesis and release is promising. However, the pharmacological actions as well as their side-effects should be identified before prescribing these medications in routine clinical practice.

Conclusions

As reported by Keim (2004), 'pain management and even more important, pain prevention are given short shrift in many orthodontic training programs'. With increased apprehension from patients as well as parents and more application of common sense by orthodontists in managing these conditions, the need to streamline research in this area has become a necessity. This article has attempted to provide an overview of research developments in this field. Orthodontic researchers as well as clinicians are encouraged to give more attention to the topic and undertake more randomized clinical trials on this issue. This will help in arriving or formulating correct methods to measure, evaluate, and manage pain as well as the distress experienced by orthodontic patients. The research will help in improving not only the living standards of our patients but also the practice environment of every orthodontic clinician.

Address for correspondence

Dr Vinod Krishnan
Gourivilasam
Kudappanakunnu PO
Trivandrum
Kerala State 695043
India
E-mail: vikrishnan@yahoo.com

References

- Aihara Y, Maeda T, Hanada K, Wakisaka S 1999 Effects of morphine on the distribution of Fos protein in the trigeminal subnucleus caudalis neurons during experimental tooth movement in rat molar. *Brain Research* 819: 48–57
- Alhashimi N, Frithiof L, Brudvik P, Bakhtiet M 2001 Orthodontic movement and *de novo* synthesis of proinflammatory cytokines. *American Journal of Orthodontics and Dentofacial Orthopedics* 119: 307–312
- Asham A A, Southard K A 2004 Orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 125: 18A
- Bergius M, Kiliardis S, Berggren U 2000 Pain in orthodontics: a review and discussion of the literature. *Journal of Orofacial Orthopedics* 61: 125–137
- Bernhardt M K, Southard K A, Batterson K D, Logan H L, Baker K A, Jakobsen J R 2001 The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 120: 20–27
- Bester H, Matsumoto N, Besson J M, Bernard J F 1997 Further evidence for the involvement of the spinobulbar pathway in nociceptive process: a *c-Fos* study in the rat. *Journal of Comparative Neurology* 383: 439–458
- Bondemark L, Fredriksson K, Ilros S 2004 Separation effect and perception of pain and discomfort from two types of orthodontic separators. *World Journal of Orthodontics* 5: 172–176
- Brown D F, Moerenhout R G 1991 The pain experience and psychological adjustments to orthodontic treatment of preadolescents, adolescents and adults. *American Journal of Orthodontics and Dentofacial Orthopedics* 100: 349–356
- Burstone C J 1962 . The biomechanics of tooth movement. In: Kraus B S, Riedel R A (eds). *Vistas in orthodontics*. Lea & Febiger, Philadelphia. pp. 197–213
- Chumbley A B, Tuncay O C 1986 The effect of indomethacin (an aspirin-like drug) on the rate of orthodontic tooth movement. *American Journal of Orthodontics* 89: 312–314
- Cureton S L 1994 Headgear and pain. *Journal of Clinical Orthodontics* 28: 525–530
- Davidovitch Z 1991 Tooth movement. *Critical Reviews in Oral Biology and Medicine* 2: 411–450
- Davidovitch Z, Nicolay O F, Ngan P W, Shanfield J L 1988 Neurotransmitters, cytokines and the control of alveolar bone remodeling in orthodontics. *Dental Clinics of North America* 32: 411–435
- Deguchi T, Takeshita N, Balam T A, Fujiyoshi Y, Takano-Yamamoto T 2003 Galanin immunoreactive nerve fibers in periodontal ligament during experimental tooth movement. *Journal of Dental Research* 82: 677–681
- Dubner R 1968 Neurophysiology of pain. *Dental Clinics of North America* 22: 11–30
- Egolf R J, BeGole E A, Upshaw H S 1990 Factors associated with orthodontic patient compliance with intra oral elastics and headgear wear. *American Journal of Orthodontics and Dentofacial Orthopedics* 97: 336–348
- Erdinc A M E, Dincer B 2004 Perception of pain during orthodontic treatment with fixed appliances. *European Journal of Orthodontics* 26: 79–85
- Fernandes L M, Ogaard B, Skoglund L 1998 Pain and discomfort experienced after placement of a conventional or super elastic NiTi aligning archwire. A randomized clinical trial. *Journal of Orofacial Orthopedics* 59: 331–339
- Ferreira S H, Nakamura M, de Abreu Castro M 1978 The hyperalgesic effects of prostacyclin and prostaglandin E₂. *Prostaglandins* 16: 31–37
- Firestone A R, Scheurer P A, Bürgin W B 1999 Patient's anticipation of pain and pain-related side effects, and their perception of pain as a result of orthodontic treatment with fixed appliances. *European Journal of Orthodontics* 21: 387–396
- Fujiyoshi Y, Yamashiro T, Deguchi T, Sugimoto T, Takano-Yamamoto T 2000 The difference in temporal distribution of *c-Fos* immunoreactive neurons between the medullary dorsal horn and the trigeminal subnucleus oralis in the rat following experimental tooth movement. *Neuroscience Letters* 283: 205–208
- Furstman L, Bernick S 1972 Clinical consideration of the periodontium. *American Journal of Orthodontics* 61: 138–155
- Gianelly A A, Goldman H M (eds) 1971 Tooth movement. *Biological basis of orthodontics*. Lea and Febiger, Philadelphia, pp. 116–204
- Goldreich H, Gazit E, Lieberman M A, Rugh J D 1994 The effect of pain from orthodontic arch wire adjustment on masseter muscle electromyographic activity. *American Journal of Orthodontics and Dentofacial Orthopedics* 106: 365–370
- Grieve III W G, Johnson G K, Moore R N, Reinhardt R A, DuBois L M 1994 Prostaglandin E (PGE) and interleukin-1 beta (IL-1β) levels in gingival crevicular fluid during human orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics* 105: 369–374
- Handelman C S 1997 Nonsurgical rapid maxillary alveolar expansion in adults: a clinical evaluation. *The Angle Orthodontist* 67: 291–305

- Haynes S 1974 Discontinuation of orthodontic treatment relative to patient age. *Journal of Dentistry* 2: 138-142
- Hiroshima K, Maeda T, Hanada K, Wakisaka S 2001 Temporal and spatial distribution of Fos protein in the parabrachial nucleus neurons during experimental tooth movement in the rat molar. *Brain Research* 900: 161-173
- Hixon E H, Aitkian H, Callow G, McDonald H, Tacy R J 1969 Optimal force, differential force, and anchorage. *American Journal of Orthodontics* 55: 437-451
- Hwang J-Y, Tee C-H, Huang A T, Taft L 1994 Effectiveness of thera-bite wafers in reducing pain. *Journal of Clinical Orthodontics* 28: 291-292
- Ingersoll B D 1982 Behavioral aspects in dentistry. Appleton Century Crofts, East Norwalk, CT.
- Jasmin L, Burke A R, Card J P, Barbaum A J 1997 Transneuronal labeling of a nociceptive pathway, the spino-(trigemino)-parabrachio-amygdaloid, in the rat. *Journal of Neuroscience* 17: 3751-3765
- Jones M L 1984 An investigation into the initial discomfort caused by placement of an archwire. *European Journal of Orthodontics* 6: 48-54
- Jones M, Chan C 1992a The pain and discomfort experienced during orthodontic treatment: a randomized controlled clinical trial of two aligning archwires. *American Journal of Orthodontics and Dentofacial Orthopedics* 102: 373-381
- Jones M L, Chan C 1992b Pain in the early stages of orthodontic treatment. *Journal of Clinical Orthodontics* 26: 311-313
- Jones M L, Richmond S 1985 Initial tooth movement: force application and pain—a relationship? *American Journal of Orthodontics* 88: 111-116
- Kato J, Wakisaka S, Kurisu K 1996 Immunohistochemical changes in the distribution of nerve fibers in the periodontal ligament during an experimental tooth movement in rat molar. *Acta Anatomica* 157: 53-62
- Kehoe M J, Cohen S M, Zarinnia K, Cowan A 1996 The effect of acetaminophen, ibuprofen and misoprostol on prostaglandin E_2 synthesis and the degree and rate of orthodontic tooth movement. *The Angle Orthodontist* 66: 339-350
- Keim R G 2004 Managing orthodontic pain. *Journal of Clinical Orthodontics* 38: 641-642
- Kluemper G T, Hiser D G, Rayens M K, Jay M J 2002 Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. *American Journal of Orthodontics and Dentofacial Orthopedics* 122: 359-365
- Kvam E, Bondevik O, Gjerdet N R 1989 Traumatic ulcers and pain in adults during orthodontic treatment. *Community Dentistry and Oral Epidemiology* 17: 154-157
- Kvinsland I, Kvinsland S 1990 Changes in CGRP-immunoreactive nerve fibres during experimental tooth movement in rats. *European Journal of Orthodontics* 12: 320-329
- Kvinsland S, Heyeraas K J, Ofjord E S 1989 Effect of experimental tooth movement on periodontal and pulp blood flow. *European Journal of Orthodontics* 11: 200-205
- Kyrkanides S, O'Banion M K, Subtelny J D 2000 Nonsteroidal anti-inflammatory drugs in orthodontic tooth movement: metalloproteinase activity and collagen synthesis by endothelial cells. *American Journal of Orthodontics and Dentofacial Orthopedics* 118: 203-209
- Lew K K K 1993 Attitudes and perception of adults towards orthodontic treatment in an Asian community. *Community Dentistry and Oral Epidemiology* 21: 31-35
- Lim H-M, Lew K K K, Tay D K L 1995 A clinical investigation of the efficacy of low level laser therapy in reducing orthodontic postadjustment pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 108: 614-622
- Linares J M 1998 Visual analogue scales. *Rasch Measurements Transactions* 12: 639
- Lund J P, Lamarre Y, Lavigne G, Duquet G 1983 Human jaw reflexes. In Desmedt J E (ed.) *Motor control mechanisms in health and disease*. Raven Press, New York, pp. 739-755
- Magdalena C M, Navarro V P, Park D M, Stuari M B S, Rocha M J A 2004 *c-Fos* expression in rat brain nuclei following incisor tooth movement. *Journal of Dental Research* 83: 50-54
- Mao J J 2002 Mechanobiology of craniofacial sutures. *Journal of Dental Research* 81: 810-816
- Mao J J, Wang X, Kopper R A 2003 Biomechanics of craniofacial sutures: orthopedic implications. *The Angle Orthodontist* 73: 128-135
- Marie S S, Powers M, Sheridan J J 2003 Vibratory stimulation as a method of reducing pain after orthodontic appliance adjustment. *Journal of Clinical Orthodontics* 37: 205-208
- Melzack R 1975 The McGill pain questionnaire: major properties and scoring methods. *Pain* 1: 277-299
- Michelotti A, Farella M, Martina R 1999 Sensory and motor changes of the human jaw muscles during induced orthodontic pain. *European Journal of Orthodontics* 21: 397-404
- Mohri Y, Fumoto M, Sato-Suzuki I, Umino M, Arita H 2005 Prolonged rhythmic gum chewing suppresses nociceptive response via serotonergic descending inhibitory pathway in humans. *Pain* 118: 35-42
- Needleman H L, Hoang C D, Allred E, Hertzberg J, Berde C 2000 Reports of pain by children undergoing rapid palatal expansion. *Pediatric Dentistry* 22: 221-226
- Ngan P, Kess B, Wilson S 1989 Perception of discomfort by patients undergoing orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics* 96: 47-53
- Ngan P, Wilson S, Shanfeld J, Amini H 1994 The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics* 106: 88-95
- Ngan P W, Yiu C, Hägg U, Wei S H Y, Bowley J 1997 Masticatory muscle pain before, during, and after treatment with orthopedic protraction headgear: a pilot study. *The Angle Orthodontist* 67: 433-438
- Nicolay O F, Davidovitch Z, Shanfeld J L, Alley K 1990 Substance P immunoreactivity in periodontal tissues during orthodontic tooth movement. *Bone and Mineral* 11: 19-29
- Norevall L I, Forsgren S, Mattson L 1995 Expression of neuropeptides (CGRP, substance P) during and after orthodontic tooth movement in the rat. *European Journal of Orthodontics* 17: 311-325
- O'Connor P J 2000 Patients' perceptions before, during, and after orthodontic treatment. *Journal of Clinical Orthodontics* 34: 591-592
- Oliver R G, Knapman Y M 1985 Attitudes to orthodontic treatment. *British Journal of Orthodontics* 12: 179-188
- Pagaenelli C 1993 Pharmacological support during orthodontic therapy with a topical anti-inflammatory. *Minerva Stomatologica* 42: 271-274
- Patel V 1989 Non-completion of orthodontic treatment: a study of patient and parental factors contributing to discontinuation in the hospital service and specialist practice. Thesis, University of Wales
- Polat O, Karaman A I 2005 Pain control during fixed appliance therapy. *The Angle Orthodontist* 75: 214-219
- Polat O, Karaman A I, Durmus E 2005 Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. *The Angle Orthodontist* 75: 791-796
- Proffit W R 2000 Contemporary orthodontics, 3rd edn. The C V Mosby Company, St Louis
- Rinchuse D J 1994 Pain-free debonding with occlusal rim wax. *Journal of Clinical Orthodontics* 28: 587-588
- Roche J J, Cisneros G J, Aes G 1997 The effect of acetaminophen on tooth movement in rabbits. *The Angle Orthodontist* 67: 231-236
- Roth P M, Thrash W J 1986 Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics* 90: 132-138
- Rotter J B 1966 Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs* 80: 1-28

- Saito I, Ishii K, Hanada K, Sato O, Maeda T 1991a Responses of calcitonin gene-related peptide-immunopositive nerve fibers in the periodontal ligament of rat molars to experimental tooth movement. *Archives of Oral Biology* 36: 689-692
- Saito M, Saito S, Ngan P W, Shanfeld J L, Davidovitch Z 1991b Interleukin-1 beta and prostaglandin E are involved in the response of periodontal cells to mechanical stress *in vivo* and *in vitro*. *American Journal of Orthodontics and Dentofacial Orthopedics* 99: 226-240
- Sari E, Ölmez H, Gürten A V 2004 Comparison of some effects of acetylsalicylic acid and rofecoxib during orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics* 125: 310-315
- Scheurer P A, Firestone A R, Bürgin W B 1996 Perception of pain as a result of orthodontic treatment with fixed appliances. *European Journal of Orthodontics* 18: 349-357
- Schuster G, Borel-Scherf I, Schopf P M 2005 Frequency of and complications in the use of RPE appliances—results of a survey in the Federal State of Hesse, Germany. *Journal of Orofacial Orthopedics* 66: 148-161
- Sergl H G, Klages U, Zentner A 1998 Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. *American Journal of Orthodontics and Dentofacial Orthopedics* 114: 684-691
- Simmons K E 1994 Pain research in orthodontics. *Medical Electronics* (<http://www.iotech.com/orthod.html> on 20.11.2005)
- Simmons K E, Brandt M 1992 Control of orthodontic pain. *Journal of the Indiana Dental Association* 71: 8-10
- Smith B R, Flanary C M, Hurst L L, Rugh J D 1984 Effects of orthodontic archwire changes on masseter muscle activity. *Journal of Dental Research* 63: 258 (abstract)
- Soltis J E, Nakfor P R, Bowman D C 1971 Changes in ability of patients to differentiate intensity of forces applied to maxillary central incisors during orthodontic treatment. *Journal of Dental Research* 50: 590-596
- Steen Law S L, Southard K A, Law A S, Logan H L, Jakobsen J R 2000 An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics* 118: 629-633
- Stewart F N, Kerr W J S, Taylor P J S 1997 Appliance wear, the patient's point of view. *European Journal of Orthodontics* 19: 377-382
- Ten Cate A R, Freeman E, Dickson J B 1977 Suture development: structure and its response to rapid expansion. *American Journal of Orthodontics* 71: 622-636
- Todesco L A, Keffer M A, Davis E L, Christerson L A 1992 Effect of a social-cognitive intervention on oral health status, behavior reports and cognitions. *Journal of Periodontology* 63: 567-575
- Vandevska-Radunovic V 1999 Neural modulation of inflammatory reactions in dental tissues incident to orthodontic tooth movement—a review of the literature. *European Journal of Orthodontics* 21: 231-247
- Walker J A, Tanzer F S, Harris E F, Wakelyn C, Desiderio D M 1987 The enkephalin response in human tooth pulp to orthodontic force. *American Journal of Orthodontics and Dentofacial Orthopedics* 92: 9-16
- Walker Jr J B, Buring S M 2001 NSAID impairment of orthodontic tooth movement. *The Annals of Pharmacotherapy* 35: 113-115
- White L W 1984 Pain and cooperation in orthodontic treatment. *Journal of Clinical Orthodontics* 18: 572-575
- Williams O L, Bishara S E 1992 Patient discomfort levels at the time of debonding. A pilot study. *American Journal of Orthodontics and Dentofacial Orthopedics* 101: 313-317
- Woolf C J 1991 Generation of acute pain: central mechanisms. *British Medical Bulletin* 47: 523-533
- Yamaguchi M, Kojima T, Kanekawa M, Aihara N, Nogimura A, Kasai K 2004 Neuropeptides stimulate production of interleukin 1 β , interleukin 6 and tumor necrosis factor- α in human dental pulp cells. *Inflammation Research* 53: 199-204
- Yamasaki K, Shibata Y, Imai S, Tani Y, Shibasaki Y, Fukuhara T 1984 Clinical application of prostaglandin E₁ (PGE₁) upon orthodontic tooth movement. *American Journal of Orthodontics* 85: 508-518
- Yamashiro T, Fukunaga T, Kabuto H, Ogawa N, Takano-Yamamoto T 2001 Activation of the bulbospinal serotonergic system during experimental tooth movement in the rat. *Journal of Dental Research* 80: 1854-1857
- Yamashiro T, Satoh K, Nakagawa K, Moriyama H, Yagi T, Takada K 1998 Expression of Fos in the rat forebrain following experimental tooth movement. *Journal of Dental Research* 77: 1920-1925

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