



## **MANAGEMENT OF PAIN IN ORTHODONTIC TREATMENT- A REVIEW**

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### **ABSTRACT:**

Pain and discomfort are among the most frequent side effects of orthodontic therapy. Patients who have orthodontic pain are more likely to self-medicate with over-the-counter medications before seeing a dentist. An orthodontist must respond to questions that may arise in a clinical setting by considering the viewpoints of the physicians and the parents/patients. The mechanical stresses placed on the teeth and supporting tissues during orthodontic treatment are the main cause of orthodontic pain. It can be divided into two categories: chronic pain that may last the entire course of treatment, and acute discomfort that occurs after orthodontic modifications. Different patients have different expectations about how painful orthodontic treatment will be, so it's important to appropriately address and manage these concerns. This literature review's primary goal is to go over both contemporary as well as conventional ways of managing pain during orthodontic treatment.

**Keywords:** orthodontic pain, acute and chronic, self-medicate, mechanical stresses.

### **INTRODUCTION:**

Orthodontic consultations are frequently accompanied by pain, which is a complex experience that comprises sensations elicited by and reactions to unpleasant stimuli. Recent papers make clear that this, one of the most often reported adverse effects of orthodontic treatment, is a serious issue for both practitioners and patients<sup>1</sup>. Numerous surveys have been conducted to gauge patients' concerns regarding pain during orthodontic treatment; the results of several of these studies have indicated that pain is the main cause of treatment discontinuation<sup>2</sup>. Pain is an individualised response that is highly subjective. Age, gender, the amount of force used, the individual's pain threshold, the stress and emotional condition at the time, cultural differences, and prior pain experiences are some of the variables that affect it.<sup>3</sup>. Relatively speaking, pain begins four hours after first bonding and separator installation, intensifies over the next twenty-four hours, and subsides seven days later. Orthodontic treatment-related pain and discomfort are primarily caused by a number of reasons, including pressure, ischemia, inflammation, and swelling associated with tooth

movement. The visual analogue scale (VAS) and numerical rating scale (NRS) are the most widely used tools for assessing pain intensity. In orthodontic pain management, both pharmaceutical and non-pharmacological techniques can be employed to varying degrees<sup>4</sup>. Moreover, the discomfort associated with often wearing fixed orthodontic appliances significantly lowers the quality of life for orthodontic patients. The primary contributing factors to discomforts are typically poor dental hygiene, speech impediment, eating difficulties, tooth movement, taste impairment, halitosis, and gingival bleeding<sup>5</sup>. The type of appliance might also have an impact on the degree of pain. Compared to patients with detachable appliances, patients with fixed appliances report much higher levels of pain intensity<sup>6</sup>. In addition to other advantages that have been suggested, Invisalign aligners have been demonstrated to cause less discomfort in the early phases of treatment when compared to fixed orthodontic appliances.<sup>7</sup> The length and intensity of orthodontic pain—the two most crucial aspects—are frequently disregarded. The aforementioned operations are known to induce discomfort; however, the reason for this pain is unknown. Orthodontic procedures have been found to impair patients' proprioceptive and discriminating abilities for as long as four days<sup>8</sup>. This can lead to a decrease in pain threshold and interfere with normal mechanisms that are linked to proprioception input from periodontal ligament nerve endings. The PDL area will experience pressure, ischaemia, inflammation, and oedema simultaneously<sup>9</sup>. An author described applying orthodontic force and experiencing both immediate and delayed pain<sup>10</sup>. He related the PDL's hyperalgesia to the delayed reaction and compression to the early response. Prostaglandins (PGEs), which increase the PDL's sensitivity to secreted algogens such as histamine, bradykinin, PGEs, serotonin, and substance P, have been linked to this hyperalgesia<sup>11,12</sup>. It is evident that all orthodontic treatments will result in compression and tension zones in the PDL region, giving patients an uncomfortable experience.

## **MATERIALS AND METHODS:**

A PubMed, NCBI, google scholar, Indian Journal of Dental Sciences, and Google search was undertaken on the terms of inflammation, orthodontic pain, dental pain, analgesics, NSAIDs, anesthetics,.. The review was limited to studies published in English from the year of 1961 to 2023.

## **COMMON CAUSES OF ORTHODONTIC PAIN:**

- i. Initial stage of treatment
- ii. Intermaxillary elastics
- iii. Appliance activation
- iv. Debonding of orthodontic appliances
- v. Insertion of temporary anchorage devices
- vi. Separator placement
- vii. Banding of tooth
- viii. Initial wire placement
- ix. Retraction mechanics
- x. Extraoral appliances
- xi. Expansion of maxilla

## **PATHOPHYSIOLOGY OF PAIN ASSOCIATED TO ORTHODONTICS:**

Pain connected orthodontic tooth movement originates from the periodontal tissue due to mechanical injury causing pressure, ischemia, inflammation and edema in the pdl space producing inflammation reaction.



Reduction of proprioceptive and discriminating abilities occur after orthodontic force application for few days



Which results in lowering of pain threshold and disruption of normal mechanism associated with proprioception input from nerve ending in the periodontal ligament.



Due to diffusion various inflammatory mediators intradental nociceptive nerves gets involved, the effect of periodontal tissue injury may also be affected



All these effects are perceived as pain by the patients<sup>13</sup>

## **RELATIONSHIP OF FORCE APPLICATION WITH PAIN:**

- **FIRST DEGREE-** the patient is not aware of pain unless the orthodontist manipulates the teeth to be moved by appliances, example: using instruments such as band pusher or force gauge.
- **SECOND DEGREE-** pain or discomfort caused during clenching or heavy biting usually occurs within the first week of appliance placement. The patient can eat normally.
- **THIRD DEGREE-** If this form of pain arises, the patient may be struggling to masticate normal-consistency food.<sup>14</sup>

### **Based on time of onset pain can be immediate or delayed**

- Immediate - which is associated with sudden placement of heavy forces on the tooth, example: hard figure of 8 tie between the central incisors to close midline diastema.
- Delayed - produced by variety of force values from light to heavy and representing the hyperalgesia of the periodontal membrane. This type of pain response decreases with time, the pain reaction might start as third degree but become second or first degree of pain as time passes.

## **MECHANISM UNDERLYING THE ORTHODONTIC PAIN:**

- In effect, orthodontic pain and orthodontic tooth movement are two inter-related and dependent biological events with local inflammation being their common mechanism. The product of local inflammation (example: prostaglandin and bradykinin) act on sensory endings to initiate painful sensation.
- Therefore the mechanism underlying orthodontic pain lies in periodontal inflammatory responses induced by orthodontic forces
- The periodontal inflammatory responses include 3 components;
  - Vascular event
  - Cellular event
  - Chemical event<sup>15</sup>

## HOW ORTHODONTISTS MANAGE TO MINIMIZE THE PAIN?:

When treating patients who have a low threshold for pain, orthodontists should do a unique assessment to ascertain the least amount of force that is appropriate for them perhaps delivered gradually.

- Light force from elastic power chains, braided or shape memory orthodontic wires, and self-ligating brackets can help lessen the amount of force applied to teeth and, consequently, the amount of pain experienced by patients.
- When wearing intermaxillary elastics for the first time, two thirds of orthodontic patients experience pain. As a result, some patients take them off before eating and then "forget" to put them back on.
- Orthodontists should avoid making early occlusal contacts because certain patients may experience pain due to the trauma they generate. Chewing causes more pain, which makes some people adjust how they eat. Typically, the recommendation given to them is to consume soft foods or to eat their regular meals in tiny portions. However, in order to activate the periodontium's cells and help them fight inflammation, some authors advise orthodontic patients to chew on anything rather hard, like a sheet of plastic, in the initial few hours following an archwire adjustment<sup>16</sup>.

## TREATING PAIN IN ORTHODONTIC PATIENTS:

### Pharmacological management:

The periodontal ligament experiences areas of stress and pressure as a result of the continuous, regulated mechanical forces that are applied to the tooth during orthodontic motions. Osteocytes, cementoblasts, fibroblasts, and other clast cells experience cellular stress and occasionally inflammation, which leads to the type of bone remodeling that facilitates tooth movement. Prostaglandins and leukotrienes, two products of arachidonic acid, as well as a number of other mediators, take part in the inflammatory process during bone remodelling.<sup>17,18</sup>

MMPs, or matrix metalloproteinases, are essential for the extracellular matrix's remodeling. Increased expression of MMP-1, -2, -8, -9, and -13 as well as tissue inhibitor matrix metalloproteinase (TIMP)-1 and -3 is seen in the periodontal ligament (PDL)<sup>19,20</sup> and alveolar bone of animals used in experimental orthodontic tooth movement, primarily rats. There have been reports of a rise in MMP-2, MMP-8, and occasionally MMP-1 in the gingival crevicular fluid taken from orthodontic patients<sup>21</sup>. Additionally, MMP-13 mRNA levels have been found in rodents under stress and compression, and the expression of the MMP-13 gene appears to be variably regulated and time-dependent.<sup>22</sup>

### MEDICATIONS:

Following the application of an orthodontic force, pain and discomfort start to manifest a few hours later and remain for around five days.<sup>23</sup> Arachidonic acid (AA) is the source of prostaglandins (PGs), lipid mediators that are essential to the pathophysiology of inflammation, fever, and pain. The most widely used pharmaceuticals in the world for treating pain, inflammation, and fever are nonsteroidal anti-inflammatory drugs, or NSAIDs.<sup>24</sup> Afferent nerve impulses are blocked by preoperative analgesics before they enter the central nervous system. Ketorolac and celecoxib are NSAIDs. Similar to how celecoxib inhibits selective COX-2, and ketorolac inhibits the enzyme COX, they both prevent the creation of prostaglandin.<sup>25</sup>

Paracetamol belongs to a group of medications called "aniline analgesics."<sup>26</sup> Some sources classify it as an NSAID<sup>27,28</sup>. others, meanwhile, disagree that it qualifies as an NSAID<sup>28,29</sup>. The primary mechanism put forward is thought to involve COX inhibition, and new research indicates that this mechanism is extremely selective for COX-2<sup>29</sup>. It was believed to be blocking the expression of COX-3, a third isoform found exclusively in the brain and spinal cord. Consequently, Paracetamol has very little influence on

prostaglandin synthesis<sup>30</sup>. Patients react in extremely variable ways to this new challenge. The development of aphous ulcers in a patient, for example, might indicate an especial sensitivity to orthodontic appliances.

MILD TO MODERATE PAIN	LEVEL-1	Peripheral analgesics(non-narcotic)	Paracetamol(acetaminophen),NAIDs, Aspirin .
MODERATE TO INTENSE PAIN	LEVEL-2	Weak opiates alone or associated with level-1 analgesics	Codeine+acetaminophen, tramadol+acetaminophen Powdered opium+acetaminophen
INTENSE PAIN	LEVEL-3	Strong opiates, pure agonist,partial agonist,agonist-antagonist.	Morphine, fentanyl , buprenorphine, Nalbuphine. <sup>31</sup>

### Medications advised for children with dosage:

MEDICATIONS	DOSAGE
acetaminophen	60 mg/kg/day in 4 to 6 applications
ibuprofen	20-30 mg/ kg/ day in 3 to 4 applications
Codeine+acetaminophen	3 mg /kg/day in 4 to 6 applications + 60 mg / kg /day in 4 to 6 applications <sup>31</sup>

### Mouthwashes and gels:

Orthodontists frequently recommend mouthwashes that contain both a disinfection and an analgesic; currently, chlorohexidine mouthwashes with an additional painkiller are the most widely used. Patients should be advised by orthodontists that these products will discolour soft tissues and teeth and leave a transient taste behind. However, in order to minimise negative side effects, chlorohexidine should only be administered for a short period of time and at low dosages.

Patients can also use analgesic gel, such as Dynexan 2% with alidocaine chlorhydrate base or Pansoral's "junior orthodontic" version, to relieve irritated soft tissues. These gels lessen discomfort, but they don't last very long, and it's unclear if they have any real medicinal benefit at all<sup>32</sup>.

Recently introduced mouthwashes (such as Bioxaphte, Hyalugel, and Aftamed), sprays, and gels with a high molecular weight hyaluronic basis rapidly alleviate discomfort through a barrier effect and enhance the mucosa's ability to withstand the attack of sharp device edges. Because the sprays and gels' high molecular weight hyaluronic base triggers the body's natural tissue repair system, they cover lesions and promote healing<sup>33</sup>. As of yet, there are neither known adverse effects nor usage restrictions for them.

### Non-pharmacological management:

- Low-level laser therapy (LLLT).
- Appliance adjustments.
- Experimental chewing adjuncts, e.g. bite wafers and chewing gum.
- Psychosocial and other interventions, e.g. verbal follow-up and reassurance in the form of a structured telephone call, brain wave music or cognitive behavioural therapy.

- Physical interventions such as transcutaneous electric nerve stimulation (TENS), ice/cryotherapy and acupuncture/acupressure.

### **Vibratory forces:**

Vibratory forces are effective when used before the development of pain as they improve and re-establish the blood supply in the pain causing ischemic areas. Vibration may help relieve compression of PDL, promoting normal circulation to prevent the proliferation of inflammatory by-products.

Based on a clinical study conducted by Marie et al, have advised the use of vibratory apparatus to reduce the pain caused by orthodontic treatment<sup>34</sup>.

### **Chewing gums and bite wafers:**

Several randomized studies were conducted one such study suggested that use of chewing gum for pain caused due to orthodontic appliances. The study conducted by Farzanegan et al, They suggested the efficacy of chewing gum in reducing pain caused by orthodontic procedures was comparable to the use of analgesic. Bite wafers are made of soft acrylic material, these bite wafers are used during the debonding procedures to reduce the pain caused by the removal of brackets<sup>35,36</sup>.

### **Low level laser therapy:**

A recent systematic review demonstrated that LLLT might improve orthodontic treatment by accelerating tooth movements and modulating acute pain as well as preventing relapse.

The quality of scientific evidence supporting the use of LLLT in the treatment of acute pain was low. Besides its analgesic effect, LLLT enhances tissue recovery and accelerates tooth movement<sup>35</sup>.

### **Cryotherapy:**

Cryotherapy is a medical treatment that uses low temperatures to modulate pain transmission from tissues. It improves capillary contraction and lowers the temperature of injured areas after trauma, surgery, or both. This method may minimize edema by lowering permeability, hemorrhage, and metabolism<sup>37</sup>.

### **Orthodontic appliance Modifications:**

- The brackets' edges should be smooth and rounded, and their size should be customized to the patient's needs. Bruises and ulcerations can be caused by wings, hooks, sharp edges, twisted ligatures, and excessively large or incompletely filled bracket slots. Self-ligating brackets have attractive features that may eliminate some of these problems.
- Orthodontists should correctly adjust arch wires to the contour of the dental arches and be sure that loops bent into them are not too obtrusive. Orthodontists should be sure arch wires either do not protrude distally from the molar tube or else are bent back comfortably around them.
- Orthodontists should use elastic ligatures whenever possible, especially at the beginning of treatment, because they are less irritating than steel ligatures. But if a metal ligature is indicated, the orthodontist should be sure to tuck its end safely under the arch wire.
- The tongue can become extremely irritated by lingual or palatal appliances. When such irritation occurs, orthodontists should be sure it doesn't become infected and that the patient's suffering is promptly alleviated<sup>38,39</sup>.

### **Prevention of injuries:**

Any sharp part of an appliance that protrudes should have silicone or wax put to it, either by the patient or the orthodontist. Pliable light-cured single-component materials, like as Ivoclar Vivadent's System Inlay, are useful for covering appliances in lingual orthodontics and improving patient comfort, particularly in relation to bruise healing. When possible, the orthodontist may choose to remove the offending device until healing has occurred in cases of rather substantial injuries<sup>40,41</sup>.

## **CONCLUSION:**

Orthodontist must be aware of various factors that may cause pain or discomfort to the patients and should be able to manage such episodes to improve the compliance the patient with the orthodontic therapy. However, based on the current evidence, analgesics remain the most effective and widely used approach of pain management. Furthermore, when prescribing analgesics, orthodontists must be informed of the pharmacological action as well as the pros and disadvantages of each medicine. Each patient should be given the maximum recommended dose. Patients with specific illnesses, such as psychological discomfort or trigeminal neuralgia, frequently require collaboration with specialists and enhanced care management. Nonetheless, pain management is a complicated phenomenon. As a result, additional research integrating various approaches of orthodontic pain control with proper study designs and high sample numbers is required<sup>35</sup>.

## **REFERENCE:**

1. Oliver RG, Knapman YM. Attitudes to orthodontic treatment, *British Journal of Orthodontics*, 1985, vol. 12 (pg. 179-188) [Google Scholar](#) [Crossref](#) [PubMed](#)
2. Haynes S. Discontinuation of orthodontic treatment relative to patient age, *Journal of Dentistry*, 1974, vol. 2 (pg. 138-142) [Google Scholar](#) [Crossref](#) [PubMed](#)
3. Ngan P, Kess B, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment, *American Journal of Orthodontics and Dentofacial Orthopedics*, 1989, vol. 96 (pg. 47-53) [Google Scholar](#) [Crossref](#) [PubMed](#)
4. Koritsánszky N., Madléná M. Pain and discomfort in orthodontic treatments. Literature review. *Fogorv. Sz.* 2011;104(4):117–121. [\[PubMed\]](#) [\[Google Scholar\]](#)
5. Marques L.S., Paiva S.M., Vieira-Andrade R.G., Pereira L.J., Ramos-Jorge M.L. Discomfort associated with fixed orthodontic appliances: Determinant factors and influence on quality of life. *Dental Press J. Orthod.* 2014;19(3):102–107. doi: 10.1590/2176-9451.19.3.102-107.oar. [\[PMC free article\]](#) [\[PubMed\]](#) [\[CrossRef\]](#) [\[Google Scholar\]](#)
6. Sergl H.G., Klages U., Zentner A. Pain and discomfort during orthodontic treatment: Causative factors and effects on compliance. *Am. J. Orthod. Dentofacial Orthop.* 1998;114(6):684–691. doi: 10.1016/S0889-5406(98)70201-X. [\[PubMed\]](#) [\[CrossRef\]](#) [\[Google Scholar\]](#)
7. Fujiyama K., Honjo T., Suzuki M., Matsuoka S., Deguchi T. Analysis of pain level in cases treated with Invisalign aligner: Comparison with fixed edgewise appliance therapy. *Prog. Orthod.* 2014;15:64. doi: 10.1186/s40510-014-0064-7. [\[PMC free article\]](#) [\[PubMed\]](#) [\[CrossRef\]](#) [\[Google Scholar\]](#)
8. Soltis JE, Nakfoor PR, Bowman DC. Changes in ability of patients to differentiate intensity of forces applied to maxillary central incisors during orthodontic treatment, *Journal of Dental Research*, 1971, vol. 50(pg. 590-596) [Google Scholar](#) [Crossref](#) [PubMed](#)
9. Furstman L, Bernick S. Clinical consideration of the periodontium, *American Journal of Orthodontics*, 1972, vol. 61 (pg. 138-155) [Google Scholar](#) [Crossref](#) [PubMed](#)
10. Burstone CJ. Kraus BS, Riedel RA. The biomechanics of tooth movement, *Vistas in orthodontics*, 1962 Philadelphia Lea & Febiger (pg. 197-213) [Google Scholar](#) [Google Preview](#)
11. Ferreira SH, Nakamura M, de Abreu Castro M. The hyperalgesic effects of prostacyclin and prostaglandin E2, *Prostaglandins*, 1978, vol. 16 (pg. 31-37) [Google Scholar](#) [Crossref](#) [PubMed](#)
12. olat O, Kararam AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain, *The Angle Orthodontist*, 2005, vol. 75 (pg. 791-796) [Google Scholar](#) [PubMed](#)

13. Rakhshan H, Rakhshan V. Pain and discomfort perceived during the initial stage of active fixed orthodontic treatment. *Saudi Dent J*. 2015 Apr;27(2):81-7. doi: 10.1016/j.sdentj.2014.11.002. Epub 2015 Jan 27. PMID: 26082574; PMCID: PMC4459114.

14. Scheurer, Philipp A.; Firestone, Allen R.; Bürgin, Walter B. (1996). *Perception of pain as a result of orthodontic treatment with fixed appliances*. European journal of orthodontics, 18(4), pp. 349-357. Oxford University Press [10.1093/ejo/18.4.349](https://doi.org/10.1093/ejo/18.4.349)

15. DavidovitchZ, Nicolay OF, Ngan PW, Shanfeld JL. Neurotransmitters, cytokines and the control of alveolar boneremodeling in orthodontics, *Dental Clinics of North America*, 1988, vol. 32 (pg. 411-435)[Google Scholar](#)[PubMed](#)

16. Topolski F, Moro A, Correr GM, Schimim SC. Optimal management of orthodontic pain. *J Pain Res*. 2018 Mar 16;11:589-598. doi: 10.2147/JPR.S127945. PMID: 29588616; PMCID: PMC5859910.

17. Consolaro, A. *Reabsorções Dentárias Nas Especialidades Clínicas*. 2nd ed. Maringá, BrazilDental Press. 2005. 353–400.

18. Consolaro, A. Orthodontic treatment does not cause pulpal necrosis. *Dental Press Endod* 2011;1:14–20.[Google Scholar](#)[Crossref](#)

19. Domon, S., H. Shimokawa, Y. Matsumoto, S Yamaguchi, and K. Soma. In situ hybridization for matrix metalloproteinase-1 and cathepsin K in rat root-resorbing tissue induced by tooth movement. *Arch Oral Biol* 1999. 44:907–915.[Google Scholar](#)[Crossref](#)[PubMed](#)

20. Leonardi, R., N. F. Talic, and C. Loreto. MMP-13 (collagenase 3) immunolocalisation during initial orthodontic tooth movement in rats. *Acta Histochem* 2007. 109:215–220.[Google Scholar](#)[Crossref](#)[PubMed](#)

21. Cantarella, G., R. Cantarella, M. Caltabiano, N. Risuglia, R. Bernardini, and R. Leonardi. Levels of matrix metalloproteinases 1 and 2 in human gingival crevicular fluid during initial tooth movement. *Am J Orthod Dentofacial Orthop* 2006. 130:568.e11–16.[Google Scholar](#)

22. Takahashi, I., M. Nishimura, K. Onodera, J. W. Bae, H. Mitani, M. Okazaki, Y. Sasano, and H. Mitani. Expression of MMP-8 and MMP-13 genes in the periodontal ligament during tooth movement in rats. *J Dent Res* 2003. 82:646–651.[Google Scholar](#)[Crossref](#)[PubMed](#)

23. Aronoff, D. M., J. A. Oates, and O. Boutaud. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther* 2006. 79:9–19

24. Fernandes, L. M., B. Ogaard, and L Skoglund. Pain and discomfort experienced after placement of a conventional or a superelastic NiTi aligning archwire. A randomized clinical trial. *J Orofac Ortho* 1998. 59:331–339.[Google Scholar](#)[Crossref](#)[PubMed](#)

25. Shibasaki, T., J. H. Yozgatian, J. L. Zeredo, C. Gonzales, H. Hotokezaka, Y. Koga, and N. Yoshida. Effect of celecoxib on emotional stress and pain-related behaviors evoked by experimental tooth movement in the rat. *Angle Orthod* 2009. 79:1169–1174[Google Scholar](#)[Crossref](#)[PubMed](#)

26. Aronoff, D. M., J. A. Oates, and O. Boutaud. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther* 2006. 79:9–19.[Google Scholar](#)[Crossref](#)[PubMed](#)

27. Wagner, W., P. Khanna, and D. E. Furst. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics and drugs used in gout. In Katzung, B. G. ed. Basic and Clinical Pharmacology. 9th ed. New York, NY McGraw-Hill. 2004. 586Google Scholar

28. Bertolini, A., A. Ferrari, A. Ottani, S. Guerzoni, R. Tacchi, and S. Leone. Paracetamol: new vistas of an old drug. *CNS Drug Rev* 2006. 12:250–275.Google ScholarCrossref PubMed

29. Hinz, B., O. Cheremina, and K. Brune. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* 2008. 22:383–390.Google ScholarCrossref PubMed

30. Roche, J. J., G. J. Cisneros, and G. Acs. The effect of acetaminophen on tooth movement in rabbits. *Angle Orthod* 1997. 67:231–236.Google ScholarPubMed

31. Ngan P, Wilson S, Shanfeld J, Amini H. The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *Am J Orthod Dentofacial Orthop*. 1994 Jul;106(1):88-95. doi: 10.1016/S0889-5406(94)70025-7. PMID: 8017354.

32. Naim, M., Hasan, M., Nahar, L., Nasrin, T., Naznin, S., & Ghosh, R. (2016). Causes of Orthodontic Pain & its treatment: an overview. *Update Dental College Journal*, 6(1), 43–51. <https://doi.org/10.3329/updcj.v6i1.29220>

33. D'Agostino A, Stellavato A, Corsuto L, Diana P, Filosa R, La Gatta A, et al. Is molecular size a discriminating factor in hyaluronan interaction with human cells? *Carbohydrate polymers*. 2017;157:21–30.

34. Lobre WD, Callegari BJ, Gardner G, Marsh CM, Bush AC, Dunn WJ. Pain control in orthodontics using a micropulse vibration device: A randomized clinical trial. *Angle Orthod*. 2016 Jul;86(4):625-30. doi: 10.2319/072115-492.1. Epub 2015 Oct 23. PMID: 26496680; PMCID: PMC8601487.

35. Hussain AS, Al Toubity MJ, Elias WY. Methodologies in Orthodontic Pain Management: A Review. *Open Dent J*. 2017 Aug 31;11:492-497. doi: 10.2174/1874210601711010492. PMID: 28979577; PMCID: PMC5611706.

36. Williams OL, Bishara SE. Patient discomfort levels at the time of debonding: a pilot study. *Am J Orthod Dentofacial Orthop*. 1992 Apr;101(4):313-7. doi: 10.1016/S0889-5406(05)80324-5. PMID: 1558060.

37. Padhraig S. Fleming, D. Al-Moghrabi, P. Fudalej, N. Pandis Orthodontic pain: The use of nonpharmacological adjuncts and its effect on compliance,Seminars in Orthodontics,Volume 24, Issue 2,2018,Pages 248-258,ISSN 1073-8746,https://doi.org/10.1053/j.sodo.2018.04.007.

38. Artun J, Brobakken BO (1986) Prevalence of carious white spots aier orthodontic with multibonded appliances. *Eur J Orthod* 8: 229-234.

39. Morrow D, Wood DP, Speechley M (1992) Clinical effect of subgingival chlorhexidine irrigation on gingivitis in adolescent orthodontic patients. *Am J Orthod Dentofacial Orthop* 101: 408-413.

40. Zachrisson BU, Zachrisson S (1972) Gingival condition associated with partial orthodontic treatment. *Acta Odontologica Scandinavica* 30: 127-136.

41. Zachrisson BU, Zachrisson S (1971) Caries incidence and oral hygiene during orthodontic treatment. *Eur J Oral Science* 79: 394-401.

