ORIGINAL RESEARCH

Correlation between Pain Perception and CGRP Expression during Initial Tooth Alignment Using either a Self-ligating or a Pre-adjusted Bracket System

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Abstract

Aim and objective: Orthodontic tooth movement (OTM) occurs when the force applied to the tooth stimulates inflammation and alveolar bone remodeling. Less friction is produced by passive self-ligating (PSL) brackets compared to pre-adjusted edgewise (PE) brackets; therefore, PSL bracket use is thought to result in less pain than the use of PE brackets. The neuropeptide calcitonin gene-related peptide (CGRP), isolated from gingival crevicular fluid (GCF), can be used as a pain biomarker for OTM. Pain perception can be subjectively evaluated using the visual analog scale (VAS). This study aimed to analyze pain perception, using the VAS and CGRP levels, and to examine the correlation between VAS scores and CGRP levels.

Materials and methods: A total of 15 patients were included in this study (a PSL group, a PE group, and a control group). GCF was collected from the lower anterior teeth, at interproximal sites, before bracket insertion and 2 hours, 24 hours, and 168 hours after lower archwire engagement. Pain perception was recorded using the VAS. CGRP concentrations were analyzed using an enzyme-linked immunosorbent assay (ELISA).

Results: The VAS scores of the PE and PSL groups increased 2 hours after archwire engagement, peaked after 24 hours, and returned to baseline after 168 hours, and the PE group had high scores than the PSL group, with the highest score being recorded at the 24 hour time point. CGRP concentrations were also the highest at the 24 hour time point compared to the other time points.

Conclusion: These results showed that both the VAS score and the CGRP concentration increased during initial orthodontic tooth alignment when using either the PSL or the PE bracket systems. Pain perception scores and CGRP concentrations were weakly positively correlated.

Clinical significance: The type of bracket system used influenced the patients' pain perception scores and the release of CGRP.

Keywords: Calcitonin gene-related peptide, Cohort study, Orthodontic tooth movement, Pain, Passive self-ligating, Pre-adjusted.

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Introduction

The application of orthodontic force to teeth produces inflammation and pain.[1] Orthodontic treatments using passive self-ligating (PSL) brackets result in less friction and were shown to cause less pain than the use of pre-adjusted edgewise (PE) brackets.[2–4] Histological studies during orthodontic tooth movement (OTM), conducted by Reitan (1965),[5] showed that lighter force is less traumatic and more efficient; therefore, the applied force may be correlated with pain perception levels.

The frictional resistance that occurs during OTM consists of complex interactions between the archwire, the bracket, and the method of ligation. PSL and PE brackets utilize different ligation systems. PSL brackets use a built-in mechanical device to hold the wire in the slot, whereas PE brackets use wire ligatures to hold the wire in the slot. Without the wire ligature, the friction between the bracket and the archwire in the PSL bracket decreases significantly, requiring less force to move teeth compared to the PE bracket.[2,3,6]

Pain can discourage patients from seeking orthodontic treatment. Pain perception can be influenced by psychological, sociocultural, gender, age, and environmental factors, which are subjective and difficult to measure.[7–9] The visual analog scale (VAS) is the most reliable method for measuring pain perception during orthodontic treatment.[10] Because VAS results are subjective, orthodontists can have difficulty comparing pain perception levels between PSL and PE bracket systems. Neuropeptide expression increases near areas of inflammation, including inflammation caused by orthodontic force. A study conducted by Bolanos et al.[11] showed that the application of orthodontic force can stimulate local neurogenic responses, increasing the release of neuropeptides, such as substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP).[11,12] These neuropeptides induce vasodilatation and increase vascular permeability, resulting in a condition called neurogenic inflammation.[13–15]

The aim of this study was to determine the correlation between CGRP concentrations and pain perception (as measured by the VAS score) during initial alignment when using either PSL (Damon Q, Ormco) or PE (Mini Diamond MBT, Ormco) brackets.

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Materials and Methods

Ethical approval for this prospective clinical trial was obtained from the Research Ethics Committee of Universitas Indonesia (No: 28/Ethical Approval/FKGUI/III/2019). The study group included 15 patients who were divided into the following 3 groups: the PSL group, the PE group, and the control group. Patients were treated in the orthodontic clinic at Universitas Indonesia Dental Hospital. The inclusion criteria were as follows: (1) male or female individuals, aged 18–35 years old, who have not received previous orthodontic treatment; (2) lower anterior little irregularity index value between 4 and 6 mm; (3) patient who received orthodontic treatment, using either PSL (Damon Q™, Ormco) or PE (MBT, Ormco) brackets; (4) healthy periodontal tissues with generalized probing depths <3 mm; (5) good general health; (6) the absence of anti-inflammatory drug administration during the previous 6 months; and (7) a lack of antibiotic therapy during the previous 6 months. All subjects provided signed informed consent after an explanation of the study protocol.

Experimental Design

The sulcus-probing depth, presence of plaque, and bleeding on probing were evaluated for each patient. Gingival crevicular fluid (GCF) samples and VAS scores were collected at 0, 1 hour, 24 hours, and 168 hours after archwire insertion as found that the highest discomfort recorded at 24 hours and return to baseline after 168 hours.[6] The samples were collected by, using the following procedure: (1) an oral hygiene index score was assessed; (2) patients were asked for a VAS score; and (3) a GCF sample was obtained from the interproximal area of the lower anterior teeth.

Visual Analog Scale (VAS) Score

Subjects were provided with instructions and asked to record their perceived pain levels using a 100 mm VAS scale, prior to archwire insertion and 1 hour, 24 hours, and 168 hours after archwire insertion. The VAS score is the distance, in mm, from the left side of the line to the subject's mark. Each VAS score was measured twice by the same operator, with the mean taken as the representative value.

Gingival Crevicular Fluid (GCF)

Initially, the lower anterior teeth were cleaned with water, isolated using cotton rolls (to minimize saliva contamination), and air-dried. A paper point (Diadent, Korea) was inserted 1 mm into the gingival sulcus for 60 seconds. Then, the paper point was placed inside an Eppendorf tube containing 400 µL phosphate-buffered saline (PBS) and stored at –20°C, until further processing.

Enzyme-linked Immunosorbent Assay (ELISA)

The CGRP levels were measured using an ELISA kit (Phoenix Pharmaceuticals Inc, Burlingame, CA, USA), with the results expressed in pg/mL.

Statistical Analysis

Statistical analysis was performed using Special Package for Special Science (SPSS) ver. 25.0. A Friedman test was used to compare the mean VAS scores and the CGRP concentrations among the four time points for each experimental group. A parametric one-way analysis of variance (ANOVA) was used to compare the CGRP concentrations between the PE, PSL, and control groups. A nonparametric Mann-Whitney *U* test was used to compare the VAS scores between the PE and the PSL groups. The relationship between the two variables was assessed using Spearman's rank correlation coefficient. The level of statistical significance was predetermined at p value < 0.05.

Results

A total of 15 subjects were enrolled in this study and were equally distributed into PE, PSL, and control groups. Mean irregularity index scores of 6.81 ± 2.33, 5.84 ± 1.14, and 6.99 ± 2.14 mm were assessed for the PSL, PE, and control groups, respectively. All subjects maintained good oral hygiene and good periodontal statuses throughout the study.

Evaluation of Pain Perception

The mean VAS scores for both experimental groups are given in Table 1, and a pattern was observed as shown in Figure 1. The highest VAS score for each group was recorded 24 hours following bracket placement and archwire engagement. The PE group had higher mean VAS scores than the PSL group at each time point. However, the difference between VAS scores between the two groups was only significant at the 24 hour time point.

Evaluation of CGRP Concentrations

Table 2 shows the CGRP concentrations for both experimental groups and the control group. Different baseline CGRP concentrations were found among the three groups, although these differences were not statistically significant. An increase in the CGRP concentration was observed 2 hours after archwire engagement, the concentration reduced after 24 hours and then increased again after 168 hours for both experimental groups. No statistically significant differences in CGRP concentrations were observed between the experimental groups and the control group.

Table 1: Mean VAS scores of the PE and PSL groups

	PE group	*PSL group*	*p value*
Before	0.00 (0.00)	0.00 (0.00)	
After 2 hours	10.10 (14.74)	8.00 (10.36)	0.754
After 24 hours	31.20 (25.31)	19.10 (37.39)	0.028*
After 168 hours	13.70 (17.25)	4.30 (6.64)	0.074

*Significant ($p < 0.05$)

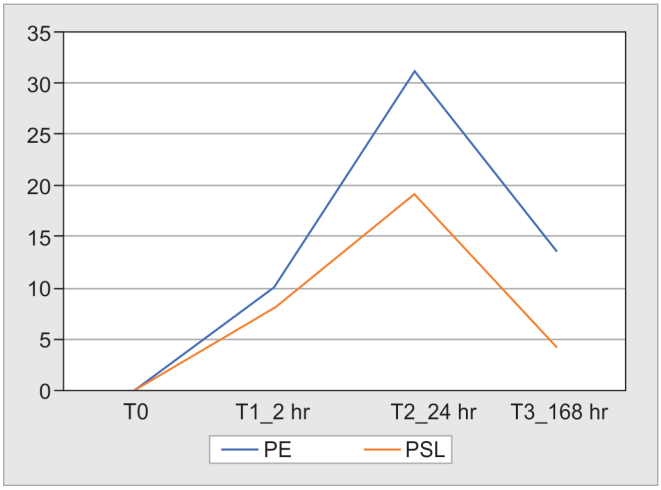

Fig. 1: Changes in pain intensity (VAS scores) for the PE and PSL groups at each time point

Table 2: CGRP concentrations of the PE, PSL, and control groups (pg/mL)

	PE group	*PSL group*	*Control group*	*p value*
Before	91.48 (69.74)	71.45 (42.99)	86.99 (73.32)	0.873
After 2 hours	95.10 (79.59)	90.23 (82.39)	76.36 (57.42)	0.918
After 24 hours	54.31 (50.23)	62.69 (47.87)	77.68 (72.30)	0.733
After 168 hours	109.29 (74.50)	83.30 (66.47)	71.09 (60.38)	0.651

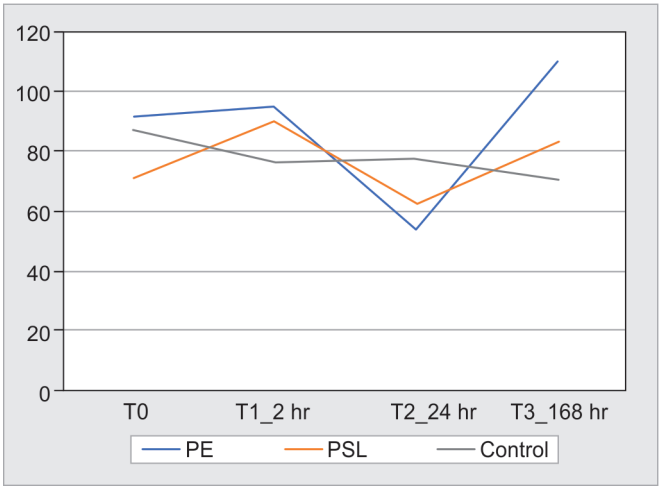

Fig. 2: Changes in the CGRP concentrations measured in GCF samples from the PE, PSL, and control groups

Relationship between Pain Perception and CGRP Concentration

Spearman's correlation coefficient showed no correlation between pain perception and CGRP concentration ($r = 0.067$; p value > 0.05).

Discussion

Pain intensity (as measured by the VAS score), in this study, increased starting 2 hours after archwire engagement, with the highest score recorded after 24 hours, followed by a return to baseline after 168 hours (Fig. 1). Giannopoulou et al.[16] reported that the initial OTM when using an elastic separator resulted in increased pain intensity after 1 and 24 hours, with a return to baseline after 24 hours. A study by Bergius et al.[17] reported that the highest pain intensity when using a conventional orthodontic fixed appliance occurred after 24 hours and began to decline after 72 hours.

The pain intensity (as measured by the VAS score) of the PE group was higher than that of the PSL group for all time points. Tecco et al.[18] compared pain perception between the use of self-ligating and conventional orthodontic fixed appliances and found that the reported pain intensity when using the self-ligating bracket was lower than that when using the conventional bracket. Similarly, our study found that the pain intensity (as measured by the VAS score) in the PE group was higher than that for the PSL group, for all time points, and this difference was statistically significant for the 24 hour time point (Table 1).

A study by Caviedes-Bucheli et al.[19] showed that the concentrations of the neuropeptides SP, CGRP, and NKA increased during pulpitis. A study in mice, performed by Noreval et al.,[20] showed that CGRP and SP concentrations in the dental pulp increased significantly compared to the control group after orthodontic force was applied. Neuropeptides that originate in the dental pulp can be transferred to the gingival crevice by dentinal fluid; therefore, in this study, samples were taken from the GCF.[21,22] The results (Fig. 2) showed increases in the CGRP concentrations 2 hours after orthodontic force was applied, for both experimental groups, although these increases were not statistically significant. These differing results are likely due to the use of different methodologies between our study and previous studies, which evaluated pulpal samples from permanent teeth. Because CGRP is a neuropeptide that is released from C-type nerve fibers, which can be found in the dental pulp, the long diffusion pathway to the GCF may lower the concentration.[21] Therefore, a slight, nonsignificant increase in CGRP expression found in the GCF may indicate that moderate orthodontic forces are correlated with reduced damage to pulp tissues.[23–25]

Sattari et al.[26] found that SP and CGRP levels in the pulp were significantly higher during symptomatic irreversible pulpitis than during asymptomatic irreversible pulpitis or in healthy pulp. Studies conducted by Awawdeh et al.[12] and Bolanos et al.[11] also showed positive correlations between CGRP and pain perception (as measured by the VAS score), and a similar correlation was found in our study. We also found a shift in the pain perception pattern compared to the CGRP concentration pattern. The maximum mean score for pain perception (as measured by the VAS score) was recorded 24 hours after archwire placement, whereas the maximum mean CGRP concentration was observed 2 hours after archwire placement. This difference is likely due to a delayed pain response, which can occur after the application of orthodontic force, as supported by the Lassen et al.[27] study that showed delayed migraine pain occurring 60 minutes to 12 hours after a CGRP infusion. CGRP is an abundant transmitter in the perivascular sensory trigeminal nerve fiber and colocalizes with SP and other neurotransmitters.[28–30] The release of this neurotransmitter occurs following sensory nerve fiber stimulation, which increases the sensitivity of the nerve terminal, resulting in a delay that can be measured in hours.[31–33] This study has potential limitation regarding sample size which could affect the reproducibility of the result.

Conclusion

In this study, the CGRP concentration was found to increase early during orthodontic tooth alignment, likely associated with periodontal inflammation caused by mechanical force. The type of bracket system used also influenced the patients' pain perception values and the concentrations of CGRP that were released. CGRP levels also had a weak positive correlation with pain perception scores; however, the pain response appeared to be slightly delayed with respect to changes in the CGRP levels. Since there are limitation in sample size of this study, for future research, it is suggested to increase the sample size and observation time.

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References

1. Lowney J, Norton L, Shafer D, et al. Orthodontic forces increase tumor necrosis factor alpha in the human gingival sulcus. Am J Orthod Dentofac Orthod 1995;108(5):519–524. DOI: 10.1016/s0889-5406(95)70052-8.
2. Proffit WR, Fields HW, Sarver DM. Contemporary orthodontics. In: Proffit WR, Fields HW, Sarver DM, eds. Contemporary orthodontics. 5th ed. USA: Elsevier; 2015. pp. 375–376.
3. McLaughlin, Bennett, Trevisi. Systemized orthodontic treatment mechanics. London: Mosby; 2001.
4. Cobourne M, DiBiase A. Management of permanent dentition. In: Handbook of orthodontics. Philadelphia: Mosby; 2010. pp. 427–434.
5. Reintan K. Selecting forces in orthodontics. Trans Eur Orthodontic Soc 1956;32:309–317.
6. Cobourne M, DiBiase A. Orthdontic tooh movement. In: Handbook of orthodontic. 2nd ed., 2016. pp. 134–143.
7. Erdinc A, Dincer B. Perception of pain during orthodontic treatment with fixed appliances. Eur J Orthod 2004;26(1):79–85. DOI: 10.1093/ejo/26.1.79.
8. Fleming PS, Johal A. Self-ligating brackets in orthodontics: A systematic review. Angle Orthod 2010;80(3):575–584. DOI: 10.2319/081009-454.1.
9. Scott P, Sherriff M, DiBiase AT, et al. Perception of discomfort during initial orthodontic tooth alignment using a self-ligating or conventional bracket system: A randomized clinical trial. Eur J Orthod 2008;30(3):227–232. DOI: 10.1093/ejo/cjm131.
10. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005;14(7):798–804. DOI: 10.1111/j.1365-2702.2005.01121.x.
11. Chavarría-Bolaños D, Martinez-Zumaran A, Lombana N, et al. Expression of substance P, calcitonin gene-related peptide, B-endorphin and methionine-enkephalin in human dental pulp tissue after orthodontic intrusion: A pilot study. Angle Orthod 2014;84(3):521–526. DOI: 10.2319/060313-423.1.
12. Awawdeh L, Lundy F, Shaw C, et al. Quantitative analysis of substance P, neurokinin A and calcitonin gene-related peptide in pulp tissue from painful and healthy human teeth. Int Endod J 2002;35(1):30–36. DOI: 10.1046/j.1365-2591.2002.00451.x.
13. Cascasco A, Calligaro A, Casasco M, et al. Peptidergic nerves in human dental pulp. Histochemistry 1990;95(2):115–121. DOI: 10.1007/BF00266583.
14. Wakisaka S. Neuropeptides in the dental pulp: distribution, origins and correlations. J Endod 1990;16(2):67–69. DOI: 10.1016/S0099-2399(06)81566-9.
15. Goodis H, Saeki K. Identification of bradykinin, substance P, and Neurokinin A in human dental pulp. J Endod 1997;23(4):201–204. DOI: 10.1016/S0099-2399(97)80045-3.
16. Giannopoulou C, Dudic A, Kiliaridis S. Pain discomfort and crevicular fluid changes induced by orthodontic elastic separators in children. J Pain 2006;7(5):367–376. DOI: 10.1016/j.jpain.2005.12.008.
17. Bergius M, Berggren U, Kiliaridis S. Experience of pain during an orthodontic procedure. Eur J Oral Sci 2002;110:92–98. DOI: 10.1034/j.1600-0722.2002.11193.x
18. Tecco S, D'Attilio M, Tete S, et al. Prevalence and type of pain during conventional and self-ligating orthodontic treatment. Eur J Orthod 2009;31:380–384.
19. Caviedes-Bucheli J, Lombana N, Azuero-Holguin M, et al. Quantification of neuropeptides (calcitonin gene-related peptide, substance P, neurokinin A, neuropeptide Y and vasoactive intestinal polypeptide) expressed in healthy and inflamed human dental pulp. Int Endod J 2006;39(5):394–400. DOI: 10.1111/j.1365-2591.2006.01093.x.
20. Norevall LI, Forsgren S, Matsson L. Expression of neuropeptides (CGRP, Substance P) during and after orthodontic tooth movement in the rat. Eur J Orthod 1995;17(4):311–325. DOI: 10.1093/ejo/17.4.311.
21. Ghazi A, Shuttleworth S, Angulo S, et al. Gallium diffusion in human root dentin: Quantitative measurements by pulsed Nd : YAG laser ablation combined with an inductively coupled plasma mass spectrometer. J Clin Laser Med Surg 2000;18(4):173–183. DOI: 10.1089/10445470050144029.
22. Walton R, Langeland K. Migration of materials in the dental pulp of monkeys. J Endod 1978;4(6):273–277. DOI: 10.1016/S0099-2399(78)80171-X.
23. Derringer K, Jaggers D, Linden R. Angiogenesis in human dental pulp following orthodontic tooth movement. J Dent Res 1996;75(10):1761–176. DOI: 10.1177/00220345960750100901
24. El Karim I, Linden G, Irwin C, et al. Neuropeptides regulate expression of angiogenic growth factors in human dental pulp fibroblasts. J Endod 2009;35(6):829–833. DOI: 10.1016/j.joen.2009.03.005
25. Caviedes-Bucheli J, Ardila-Pinto J, Del Toro-Carreño H, et al. The effect of orthodontic forces on calcitonin gene-related peptide expression in human dental pulp. J Endod. 2011;37(7):934–937. DOI: 10.1016/j.joen.2011.03.035.
26. Sattari M, Mozayeni M, Matloob A, et al. Substance P and CGRP expression in dental pulps with irreversible pulpitis. Aust Endod J 2010;36(2):59–63. DOI: 10.1111/j.1747-4477.2009.00186.x.
27. Lassen L, Haderslev P, Jacobsen V, et al. CGRP may play a causative role in migraine. Cephalalgia 2002;22(1):54–61. DOI: 10.1046/j.1468-2982.2002.00310.x
28. Buzzi M, Carter W, Shimizu T, et al. Dihydroergotamine and sumatriptan attenuate levels of CGRP in plasma in rat superior sagittal sinus during electrical stimulation of the trigeminal ganglion. Neuropharmacology 1991;30(11):1193–1200. DOI: 10.1016/0028-3908(91)90165-8
29. Limrroth V, Curtrer F, Moskowitz M. Neurotransmitters and neuropeptides in headache. Curr Opin Neurol 1996;9(3):206–210. DOI: 10.1097/00019052-199606000-00009.
30. Goadsby P, Edvinsson L. The trigeminovascular system and migraine; studies characterizing cerebrovascular and neuro-peptide changes seen in humans and cats. Ann Neurol 1993;33(1):48–56. DOI: 10.1002/ana.410330109.
31. Meller S, Gebhart G. Nitric oxide (NO) and nociceptive processing in the spinal cord. Pain 1993;52(2):127–136. DOI: 10.1016/0304-3959(93)90124-8.
32. Cumberbatch M, Williamson D, Masin G, et al. Dural vasodilation causes a sensitization of rat caudal trigiminal neurones in vivo that is blocked by a 5HT 1B/1D agonist. Br J Pharmacol 1999;126(6):1478–1486. DOI: 10.1038/sj.bjp.0702444.
33. Thomsen L, Kruuse C, Iversen H, et al. A nitric oxide donor(Nitroglycerin) triggers genuine migraine attacks. Eur J Neurol 1994;1(1):73–80. DOI: 10.1111/j.1468-1331.1994.tb00053.x.