Pain Confirmation with Neurokinin A Level During Early Orthodontic Treatment Using Pre-Adjusted Edgewise and Self-Ligating System

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Abstract

The aims of this study is to evaluate the relationship between pain perception and neurokinin A (NKA) level in orthodontic patients using passive self-ligating (PSL) and preadjusted edgewise appliance (PEA).

15 patients were enrolled into the study (PSL patient group, PEA patient group, and a control group). Gingival crevicular fluid (GCF) was collected before bonding (T0), 2 hours (T1), 24 hours (T2), and 168 hours (T3) after archwire engagement. Pain perception was recorded using the Visual Analog Scale (VAS). NKA was estimated using ELISA test.

Statistical analysis used: Mann-Whitney test was used to compare VAS score between group subjects at T0, T1, T2, and T3. Repeated ANOVA was used to compare NKA concentration between the two group.

There were significant differences between the VAS during the initial alignment using both brackets at T0, T1, T2, and T3. However, no significant differences were found between the two systems. There was an increase in NKA level after archwire engagement in both groups, though this was not statistically significant.

Orthodontic tooth movement may trigger neuropeptide, such as NKA released in GCF. Although not statistically significant, the PEA group consistently show a higher VAS than the PSL group.

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Introduction

Pain is a subjective experience that consists of sensory factors that represent the extent of the underlying disease and affective factors that portray psychological state. Patients undergoing orthodontic treatment report pain during orthodontic treatment that peak at 24 hours after appliance activation.[1] The pain associated with orthodontic treatment generally refers to uncomfortable sensations during tooth movement. Pain is a noxious stimuli that results from the force exerted by orthodontic appliances.[2] Pain perception, according to Burstone, may vary widely even when the same and equal force is applied.[3]

Tools available for the measurement of pain as the Visual Analog Score (VAS), Numerical Rating Scale, and Verbal Rating Scale are self-reporting tools.[4] The VAS is known to be a reliable, valid, and consistent tool.[5] Its use as a measuring instrument for pain relies on a self-reporting system, hence, it is very subjective. Confirmation of pain level is usually needed with the use of an objective pain-measuring tool.

Orthodontic treatment with a fixed appliance involves the selection of a bracket, archwire, and ligation system.[6] A bracket system with tip and torque prescription for each tooth known as preadjusted edgewise bracket was introduced by Andrew in 1972.[7] McLaughlin, Bennett, and Trevisi re-examined Andrews' original findings and created the MBT

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preadjusted bracket system.[7] Another available eminent bracket system is the passive self-ligating (PSL) bracket system. The PSL bracket system is believed to have the capacity to deliver optimum force due to a lower friction and enabling relatively faster tooth movement.[8-10]

Orthodontic force initiates teeth movement within the periodontal ligament space. Vascular changes due to orthodontic force triggers an inflammatory response such as recruitment of inflammatory cells and the release of neurogenic and pro-inflammatory mediators.[11] Previous research has found an elevation of neuropeptides released in patients who experience pain during orthodontic treatment.[12] Neuropeptides are active peptides that are produced in neurons. Substance P and Neurokinin A (NKA) are parts of the tachykinin family and act as regulatory peptides. NKA is one of the main neurotransmitters that are in charge of transferring moderate to severe pain signals.[12] It is known to be present in nerve fibers of the dental pulp and periodontal tissue. Pain in the dental pulp raises NKA level in the gingival crevicular fluid (GCF).[13-14] However, NKA level in the inflammatory process during fixed orthodontic treatment is unknown. Therefore, this study seeks to investigate the relationship between the pain perceived by patients undergoing fixed orthodontic treatment through the preadjusted and PSL bracket systems using the VAS and its correlation with NKA level in the GCF at 2 hours, 24 hours, and 168 hours after archwire engagement.

Materials and methods

Orthodontic patients at the University of Indonesia Dental Hospital were selected if they met the following criteria: (1) were male or female with an age range of 18–35 years, (2) had moderate crowding in the mandibular anterior teeth with Little's Irregularity Index of 4–6 mm, (3) had a good oral hygiene and healthy periodontal tissue, (4) had a good overall health condition, (5) have not used anti-inflammatory drugs for the past four months before sample collection.
Informed consent was obtained from the patients prior to the enrollment in this study. The human participant protocol was reviewed and approved by the Institutional Ethical Committee of the Faculty of Dentistry, University of Indonesia (Ref No. 26/*Ethical Approval*/FKGUI/III/2019).

Fifteen subjects were included in this study based on the mean value from similar previous study done by Giannopoulou *et al.*[15] The description of the sample size estimation was revised accordingly: G*Power application, using the F tests between groups formula settings with estimated effect size of 1 between groups, 80% statistical power, and alpha of 0.05".

Selected subjects were divided into three groups: five patients who were treated using the preadjusted edgewise bracket (MBT, Ormco, USA) were assigned to the PEA group, five patients who were treated using the passive self-ligating bracket(Damon Q^{TM}, Ormco, USA) were assigned to the PSL group, and five untreated patients were assigned to the control group. After bracket bonding, CuNiTi.014 (Ormco, USA) was inserted and ligated as the initial wire in the mandibular arch. Scaling was done a week before sample collection to all the subjects to equate the oral hygiene index.

GCF sample collection was done at four different times: before bracket placement, 2 hours after archwire engagement, 24 hours after archwire engagement, and 168 hours after archwire engagement from six anterior mandibular teeth. GCF sampling was performed after the area was isolated using cotton rolls and saliva ejector. A #30 paper point (Dentplus+, Diadent) was then inserted at 1 mm into the gingival crevice and left for 60seconds. The paper point was then stored in 400 ml Phosphate-Buffered Saline and stored at–20°C until the enzyme-linked immunosorbent assay (ELISA) test was performed. At each visit before sample collection, the oral hygiene index was measured and the subjects were given the VAS questionnaire.

Subjects were informed about how to fill the VAS questionnaires and asked to draw a vertical line in the VAS line from the left to indicate no pain and to the right to indicate severe pain based on their pain perception. The VAS score was obtained from measuring the length from the start point to the vertical line drawn by the patients/subjects using a ruler.
Neurokinin A concentration was quantified using ELISA kit (Phoenix Pharmaceuticals Inc, USA) in pg/mL.

Results

Fifteen subjects consisting of 8 males and

7 females with a mean age of 24.13 ± 4.12 years who fulfilled the inclusion criteria were included in this prospective clinical trial. Little's irregularity index was used to determine the inclusion criteria. Intra-observer reliability test regarding pain perception using Interclass Correlation Coefficient showed good agreement (r=1,00; 95% CI).

This study hypothesis are there were significant differences in pain perception during the fixed orthodontic initial alignment using PE and PSL bracket system at before treatment, 2 hours, 24 hours, and 168 hours after archwire placement and there were correlation between pain perception and NKA concentration using the two systems.

Following archwire placement, VAS scores in the PSL group increased at T1 and T2 and declined at T3 near the baseline (T0). Mann-Whitney test was used to compare the VAS scores between the PSL and PEA subjects at T0, T1, T2, and T3. There were no significant differences (P > 0.05) between the VAS scores in the PSL and PEA groups at all the observation times (**Table 1**).

Time	Preadjusted Edgewise (PEA)	Passive Self-Ligating (PSL)	*p-value*
Before (T0)	0.00 (0.00)	0.00 (0.00)	
After 2 hours (T1)	10.40 (14.53)	7.00 (10.94)	0.346
After 24 hours (T2)	46.00 (25.60)	29.10 (39.10)	0.502
After 168 hours (T3)	13.90 (17.06)	3.80 (6.89)	0.173

Table 1. Mean of VAS score between PSL and PEA group at T0, T1, T2, and T3 after archwire engagement.

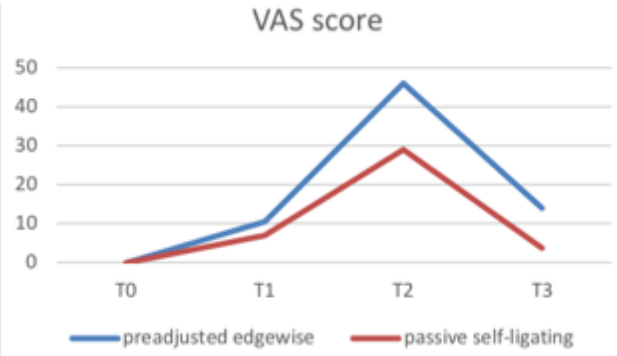

Figure 1. Graph showing pain perception in the two groups before bonding (T0), 2 hours (T1), 24 hours (T2), 168 hours (T3) after archwire placement.

Repeated ANOVA test shows no significant differences (P > 0.05) between NKA concentration in the PEA and PSL subjects at T0, T1, T2, and T3 (**Table 2**).

Time	Preadjusted edgewise (PEA)	Passive self-ligating (PSL)	Control	*p-value*
Before (T0)	4,76 (4,15)	7,56 (5,89)	7.67 (2.11)	0,505
After 2 hours (T1)	7,80 (9,46)	7,36 (5,56)	6.43 (1.80)	0,942
After 24 hours (T2)	5,46 (2,23)	7,64 (3,18)	6.98 (5.87)	0,693
After 168 hours (T3)	4,32 (4,14)	10,10 (8,05)	3.74 (4.07)	0,195

Table 2. Mean of NKA concentration (pg/mL) in PEA and PSL group at before (T0), 2 hours (T1), 24 hours (T2), and 168 hours (T3) after *archwire* placement.

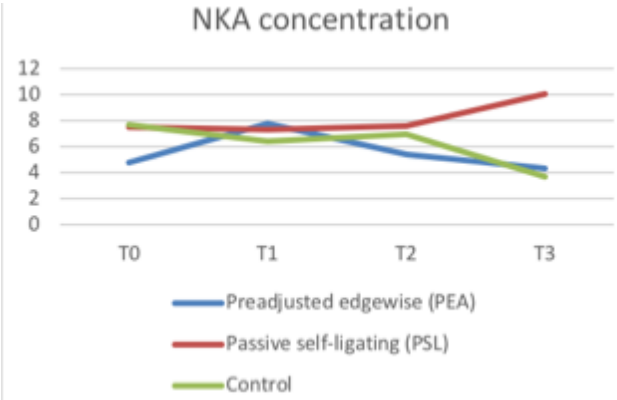

Figure 2. Graph of NKA concentration in the PEA, PSL, and control groups before bonding (T0), 2 hours (T1), 24 hours (T2), 168 hours (T3) after archwire placement.

Correlation between pain perception and NKA concentration was tested using Spearman's correlation coefficient and showed no correlation (r = −0.150; *P* = 0.254)

Discussion

Investigating pain associated with orthodontic treatment may provide insights into the development of clinical interventions that will make patients more comfortable and cooperative during orthodontic treatment. Orthodontic treatment with the use of a PSL system has been reported to have the capacity to reduce friction during tooth movement. As such, it is assumed to be capable of reducing the pain felt by patients.[16] Pain perception using the VAS in orthodontic patients treated with PSL and PEA bracket systems have been investigated by Scott, Pringle,

and Fleming.[17-19] The VAS is a reliable tool and has a good sensitivity at measuring pain perception.[20] Also, in previous study which compared VAS and Faces Pain Scale (FPS) to assess dental pain during orthodontic treatment conclude that use of VAS is considered to be more understandable by patients.[21] In this study, we used the VAS to evaluate pain perception and the results show a statistically significant difference between the scores before bonding (T0), at 2 hours (T1), at 24 hours (T2), and at 168 hours (T3) in the PEA and PSL groups. The VAS scores in both groups showed a similar pattern, though there was an increase in the pain level at 2 hours (T1), it peaked at 24 hours (T2), and decreased near the baseline at 168 hours (T3) after archwire placement. This finding is consistent with previous studies by Fernandes *et al.*, Erdinç *et al*., and Scott *et al*.[17,22,23]

A comparison of pain perception between the patients in the PSL and PEA groups shows no significant differences at any observation time. According to a study by Burrow, friction is not the main component of resistance to sliding. Rather, friction is largely a binding-release phenomenon in the PSL and PEA bracket systems.[24] Therefore, claims that the PSL bracket could reduce friction, thereby, reducing pain perception may not necessarily be true. Although the results of this study show no significant difference, the VAS scores in the PEA group were consistently higher than those of the PSL group at all of the observation times.

We found high variations in the VAS scores at T0, T1, T2, and T3, which may be due to the highly subjective nature of pain perception. Also, pain is a complex sensation that varies among individuals and has been known to be related to individual experiences, education level, socio-economy class, cultural background, and psychological status.[25]

The force from orthodontic appliances initiate local alterations in vascularity that triggers a release of various neurotransmitters, cytokines, and growth factors.[26] Any orthodontic force that causes trauma to the periodontal ligament, therefore, stimulates the release of neuropeptides such as substance P, Neurokinin A, and Calcitonin Gene Related Peptide. These neuropeptides will activate inflammatory and immune mediators and excite the afferent neuron. The afferent neuron so excited will send nerve impulses to the central nervous system and elicit pain perceived by patients.[27]

This study is probably the first to investigate the relationship between NKA and pain perception during early orthodontic tooth movement. We found an increase of in NKA concentration in the GCF in the patients in the PEA and PSL groups after orthodontic activation, though this was not statistically significant. In the PEA group, NKA concentrations increased 2 hours (T1) after archwire placement and decreased near the baseline. On the other hand, in the PSL group, we found an increase of NKA concentration 24 hours (T2) after archwire placement. An *in vitro* study by Cordasco *et al.* reported a significant effect of ligation properties on the frictional properties between ligation with PSL door slot and the elastomeric module with significantly higher frictional force found in the elastomeric module.[28] Therefore, the ligation method differences might influence the delay of neurokinin A release in the patients in the PSL group.

This is a preliminary study to know whether there are differences in NKA levels in two different braces systems and are there any tendency in increased of NKA level associated with pain. We found no correlation between the VAS scores and NKA concentration in this study. This may be due to the subjective nature of the VAS as a pain-measuring tool as well as the small sample size of this study who may also have different pain thresholds. This underscores the importance of using a larger sample in studies that use pain questionnaires such as the VAS.[19]

Conclusions

Pain perception in the patients in both groups was significantly increased at 24 hours (T2) after archwire placement and decreased at 168 hours (T3). Although pain perception between the PSL and PEA groups was not statistically significant, the PEA group consistently showed a higher VAS score than the PSL group.

NKA concentration was also increased in both the PEA and PSL groups after archwire placement, though was not statistically significant. Orthodontic tooth movement may trigger the release of neuropeptides such as NKA into the GCF.

Although the results of this study suggest that there may be no relationship between pain perception and NKA concentration, follow-up studies with a larger sample are needed to replicate and validate this idea as well as to provide additional insights into the role of NKA in orthodontic pain.

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Declaration of Interest

The authors report no conflict of interest.

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