The Oral Administration of Capsaicin Regulate Prostaglandin E2 and Endorphin Serum Level after 24 Hours of Orthodontic Tooth Movement in Wistar Rats *(Rattus Novergicus)*

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Abstract

Orthodontic tooth movement (OTM) pain sensation may affect the patient's quality of life and cooperation during orthodontic treatment using fixed orthodontic appliances.

This study aims to investigate the oral administration of capsaicin effect to Prostaglandin E2 and Endorphin serum level after 24 hours of OTM in vivo.

42 males, healthy, Wistar rats (Rattus novergicus), 14-16 weeks-old, 270-350 grams body weight were used as OTM animal model. Samples were randomly divided into 6 groups, namely normal control group (KN): healthy rats without OTM and treatment, a negative control group; KK1 group: application of OTM force, without olive oil administration as placebo; KK2 group: application of OTM force, with olive oil oral administration as placebo; KP1 group: application of OTM force, and oral adminsitration of capsaicin 15 mg/kg BW; KP2 group: application of OTM force, and oral adminsitration of capsaicin 30 mg/kg BW, KP3 group: application of OTM force, and oral adminsitration of capsaicin 45 mg/kg BW. PGE2 and endorphin serum levels analysis were conducted by means of ELISA. Shapiro-wilk test ($p>0.05$) and continued with analysis of variance (ANOVA) ($p<0.05$) with least significant different (LSD) or Mann-Whitney ($p<0.05$).

The oral administration of 15 mg Capsaicin decrease significantly PGE2 serum levels. Meanwhile, 30 mg of capsaicin administration enhance significantly endorphin serum level after 24 hours of OTM in vivo.

The oral administration of 15mg capsaicin can decrease significantly PGE2 serum level, while 30mg of capsaicin administration can enhance significantly the level of endorphin serum level after 24 hours of Orthodontic tooth movement in vivo.

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Introduction

Pain and discomfort are the most common symptom during orthodontic treatment using fixed orthodontic appliances. Pain that occurs during orthodontic tooth movement (OTM) starts within four hours, then increases over the next 24 hours, but begins to decrease at 24-48 hours and disappears within seven days after control.[1-3] Pain sensation that arises during OTM is the main reason that patients decide to stop orthodontic treatment prematurely, or it may decreased the patient's cooperative during orthodontics treatment.[1,4,5] Treatment steps that may cause pain include extraction of primary teeth, application of orthodontics separators, molar band or archwires insertion and bracket debonding.[6-10]

Orthodontic treatment aims to improve stomatognathic function, esthetic and speech rehabilitation by application of mechanical force to move the teeth into desirable position. After

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mechanical force is applied into the tooth, an inflammation occurs that stimulates the release of mediators in the periodontal tissue and pulp chamber, an interrelated vascular, cellular, neural and immunological reaction that ultimately results in the sensation of pain and the tooth moving into its socket.[11-13]

Many methods have been developed to overcome the pain that arises during OTM, both pharmacological and mechanical approaches.[13] These approaches include the administration of tramadol which belongs to the herbal active compund, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, local anesthetics topical gels, low level laser therapy (LLLT), transcutaneous electrical nerve stimulation (TENS), acupuncture and psychological approach.[14-21] Some of anti-inflammation or NSAID administration may inhibit OTM rate due to prostaglandin E2 (PGE2) levels decreased, which are inhibited to treat pain, but it has an important role in the process of bone resorption during OTM.[22] Meanwhile, the mechanical approaches have a high cost of treatment.[18,19] This has lead to a new interest in the use of herbal medicines that have been used in daily consumption such as capsaicin in chilli.

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is the active compound in chilli obtained from plants of the genus Capsicum, and is widely consumed in households to add aroma, color and taste to increase appetite. This active ingredient is in the form of a white crystalline powder which is highly volatile, hydrophobic, colorless and odorless. Capsaicin ($C_{18}H_{27}NO_3$) gives a distinctive spicy taste found in chilli and is believed to protect the plant away from herbivores and fungi.[23] The structure is non-polar so it is not soluble in water, but soluble in fats and oils. For topical application it is recommended to use sunflower oil as a solvent, while for oral application use olive oil as a solvent. From several previous studies, capsaicin is known to have anti-oxidant properties, antifungal, analgesic, anti-microbial and anti-cancer, Capsaicin has also been used in several studies dealing with pain in experimental animals.[24-31] Furthermore, in this study, the oral administration of capsaicin was done to investigate the capsaicin effect regulate the pain sensation due to OTM *in vivo* through analysis of PGE2 and endorphin level. The oral administration of capsaicin dissolved in 1 ml of olive oil was done twice with a dose of 15 mg/kg BW, 30 mg/kg BW and 45 mg/kg BW respectively to reduce pain due to 24 hours application OTM in experimental animal model.

Materials and methods

This study was an experimental laboratory study with a post-test group only control group design. This study obtained an ethical clearance from health committee of Faculty of Dental Medicine, Universitas Airlangga to conduct the research using animal model. Forthy-two male healthy Wistar rats (*Rattus novergicus*), 14-16 weeks-old, 270-350 grams body weight was used as OTM experimental animal model. The inclusion criteria for selected Wistar rats were a complete set of teeth, the maxillary and mandibular molars grew perfectly and normal mobility condition.

Capsaicin (Tokyo Chemical Industry, Japan) in powder form was dissolved in 1 ml of olive oil (*oleum olivarum*) (MCE, USA) and administered to Wistar rats orally by means of oral gavage using a syringe and feeding tube number 8 (Terumo, China). In addition, Wistar rats were randomly divided into 6 groups, namely normal control group (KN): healthy rats without OTM and treatment, a negative control group; KK1 group: application of OTM force, without olive oil administration as placebo; KK2 group: application of OTM force, with olive oil oral administration as placebo; KP1 group: application of OTM force, and oral adminsitration of capsaicin 15 mg/kg BW; KP2 group: application of OTM force, and oral adminsitration of capsaicin 30 mg/kg BW, KP3 group: application of OTM force, and oral adminsitration of capsaicin 45 mg/kg BW. Capsaicin or olive oil as placebo solution was given twice, 30 minutes before OTM force application and 6 hours after the first administration.

Prior to the establishment of OTM experimental animal model, wistar rats were anesthetized using rodent anesthesia (ketamine 0.07 ml/100 g BW and xylazine 0.03 ml/100 g BW). The OTM mechanical force applied to the teeth of 50 g/cm^2 was measured using a tension gauge (The Richmond Orthodontic Stress, Ormco, USA) and closed coil spring (Ortho Organizer, USA) attached to the permanent first

molar and right upper incisor with the aid of a diameter ligature wire. 0.11 mm (ligature wire, RMO) and fixed with type IX glass ionomer cement (Fuji IX, GIC).[31] The normal group (KN) was terminated immediately, while the control group and the treatment group (KK1, KK2, KP1, KP2, KP3) were terminated within 24 hours after the application of OTM mechanical force, then maxilla was resected to the first molar area. Measurement of PGE2 (E-EL-0034, Elabscience, US) and endorphine levels (E-EL-H0572, Elabscience, US) was carried out by means of enzyme linked immunosorbent assay (ELISA) technique using 3 ml of rat blood taken directly from the heart vein from each sample after 24 hours of observation and termination.

Anesthesia was performed intraperitoneally using 0.2 ml of a solution consisting of a mixture of xylazine (0.03 ml/100 g BW) and ketamine (0.07 ml/100 g BW). Measurement of PGE2 and endorphine levels was determined based on the standard curve. Optical density was measured at 450 nm using a microplate reader (Epoch, Netherlands) and total serum levels of PGE2 and endorphin were expressed in terms of mean and standard deviation in units of pg/ml. The data obtained were analyzed using the Shapiro-wilk test ($p>0.05$) continued with analysis of variance (ANOVA) ($p<0.05$) with least significant different (LSD) or Mann-Whitney using the Statistical Package for the Social Sciences 20.0 (SPSS inc, IBM Corp, Illinois, Chicago, USA).

Results

All research procedures were well tolerated by experimental animals, no toxic or allergic effects appeared during the study. There was a weight loss in experimental animals from each group ($p<0.05$) but did not significantly different between groups ($p>0.05$).

Statistical test using Kruskal-Wallis test in all groups showed a significant difference ($p<0.05$). Comparative analysis using the Mann Whitney test found no difference in PGE2 levels between the normal group (KN) and the OTM with capsaicin 15 mg (KP1), OTM with capsaicin 30 mg (KP2) and OTM with capsaicin 45 mg (KP3), but significant different between the OTM only group (K1), OTM with placebo (KK2) and OTM with capsaicin 15mg group (KP1) ($p<0, 05$). PGE2 levels in the normal group (KN) were lower than those in the KK1 group and KK2 group, meanwhile KP1 group PGE2 level was lower than KP2 group and KP3 group. The results of the analysis showed that the oral administration of capsaicin could significantly reduce PGE2 levels in the treatment group after being observed for 24 hours (Table 1).

Group	n	Level of Prostaglandin E2		p
		$\bar{x} \pm SD$	Min-max	
Negative control (KN)	7	1.121 ± 0.147^{b}	0.962-1,330	0.009*
OTM only (KK1)	7	1.878 ± 1.010^{c}	0.882-3,863	
OTM with placebo (KK2)	7	1.356 ± 0.083^{c}	1.225-1.470	
OTM with Capsaicin 15 mg (KP1)	7	0.809 ± 0.322^{a}	0.552-1.507	
OTM with Capsaicin 30 mg (KP2)	7	1.270 ± 0.289^{bc}	0.838-1.669	
OTM with Capsaicin 45 mg (KP3)	7	1.299 ± 0.169^{bc}	1.007-1.545	

Table 1. Description of the mean, standard deviation (SD) and test of differences between groups the level of PGE2 between the normal group, control group and treatment group.
Information: *significant at α=0.05 (Kruskal-Wallis test). ^{abc} Superscript showed the different between groups (Mann-Whitney test).

Group	n	Endorphin level		p
		$\bar{x} \pm SD$	Min-max	
Negative control (KN)	7	84.322 ± 23.876^{a}	57.193-129.644	0.001*
OTM only (KK1)	7	81.429 ± 8.727^{a}	72.054-97.705	
OTM with placebo (KK2)	7	114.324 ± 21.553^{b}	76.531-137.794	
OTM with Capsaicin 15 mg (KP1)	7	98.148 ± 10.816^{ab}	86.191-118.006	
OTM with Capsaicin 30 mg (KP2)	7	114.411 ± 10.888^{b}	95.975-128.447	
OTM with Capsaicin 45 mg (KP3)	7	103.587 ± 11.452^{b}	91.584-119.657	

Table 2. Description of the mean, standard deviation (SD) and test of differences between groups the level of Endorphin between the normal group, control group and treatment group.
Information: *significant at α=0.05 (Oneway Anova) ^{abc} Superscript showed the different between groups (*multiple comparisons* LSD)

Statistical analysis using ANOVA in all groups showed a significant difference ($p<0.05$). Comparative analysis of LSD found no significant difference in endorphin levels between the normal group (KN), KK1 group and KP1 group. Endorphin levels in the KK2 group was

significantly higher than KN group and KK1 group ($p<0.05$), but did not significant different when compared to the KP1 group, KP2 group and KP3 group. Endorphin levels in the normal group (KN) appeared to be slightly higher than the KK1 group, but lower than the KK2 group, while the KP2 group was higher than the KP3 group and the KP1 group. The results of the analysis showed that the administration of capsaicin could significantly increase the levels of endorphins in the treatment group after 24 hours of observation (Table 2).

Discussion

Pain sensation can be occurred during OTM due to inflammation triggered by mechanical force compression in the periodontal tissue. Prolong pain sensation duration may affect the patient's quality of life and cooperation during orthodontic treatment using fixed orthodontic appliance. Orthodontics patient's cooperation is a fundamental and important factor to obtain the desirable and ideal orthodontic treatment result.[32]

OTM trigger pain sensation usually occurs either during archwires placement, orthodontics separator application, or orthodontics brackets debonding. From previous studies, it has been stated that pain begins 4 hours after fixed orthodontics insertion, and increases to a peak after 24 hours and decreases and then disappears after 7 days. Pain sensation that arises is the result of an inflammatory process that occurs due to stimulation of nociceptors when the periodontal tissue is compressed.[4,8,22] The compressed periodontal ligament after OTM mechanical force application lead to inflammation. During the inflammation, neurotransmitter, chemokine, heat shock protein (HSP), malondialdehyde were released into the injury area. These molecules were known as Alarmin or Dangerous Associate Molecule Patterns (DAMPs) that send the signal to the Toll-like receptor-4. Those signals transmitted to the macrophage and the nuclear factor kappa-beta was activated.[33,34] Macrophage was activated then released Interleukin (IL)-1β that induce cyclooxygenase-1 and 2 (COX-1 and COX-2) and the secretion of arachidonic acid and PGE2 during initial orthodontic treatment. In the patient saliva with initial orthodontic treatment, Prostaglandin E2 and IL-1β level were elevated.[33,35]

The chemokines that released during OTM lead to chemotaxis of granulocytes. The proliferation of granulocytes increased significantly after the 24 hours of OTM. Granulocyte produced the opioid peptide, one of them is Endorphin that secreted 6 hours of OTM.[36] Endorphin may not enough to suppress the pain sensation but it may increase the threshold of pain sensation.[37]

Some of herbal medicines were used as analgesic and anti-inflammatory drug such as curcumin in *turmeric longa, Symphytum officinale L. and Aromatic lavender essential oil* treating low back pain.[38,39] Topical capsicum cream that applied to treat acute low back pain showed its potential as analgesic and anti-inflammatory drug.[39] Due to its potentiality as analgesic ability, in this study used capsaicin as active compound in capsicum to treat pain sensation that occurred after 24 hours application of OTM force *in vivo.*

Capsaicin is known to act on the transient receptor potential cation channel vanilloid subfamily member 1 (TRPV1). TRPV1 is involved in somatic and visceral peripheral inflammation, in the modulation of nociceptive inputs to spinal cord and brain stem centers, as well as the integration of diverse painful stimuli.[40] TRPV1 is an important sensory afferent, so that capsaicin administration can partially stimulate pain afferents has been studied in animal and human models for various indications. Capsaicin induce the initial neuronal excitation evoked by it is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli that known as defunctionalization. Capsaicin through TRPV1 independent is beneficial for the treatment of various diseases and conditions such as obesity, cancers, skin diseases, gastrointestinal tract diseases and cardiovascular diseases.[23] Some of oral NSAID anti-inflammatory drugs that prescribed have side effects, capsaicin administration may replace the NSAID for inflammation related diseases such as osteoarthritis.[41]

In this present study, we found that the oral administration of capsaicin with various doses (15mg, 30mg, 45mg) dissolved with olive oil can regulate PGE2 and endorphin serum level during OTM in experimental animal model (*in*

vivo). PGE2 and endorphin serum level have important role in pain sensation. This study result was in line with previous study that found capsaicin administration decreased the inflammatory molecules and PGE2 levels in lipopolysaccharide (LPS)-stimulated rats's macrophage through inactivating NFKb and blocked the IkB-a.[42]

The enhancement of endorphin secretion post oral administration of capsaicin showed that capsaicin evokes the release of endorphin, suggesting activation of the endorphin terminal systems.[43] The enhancement of endorphin serum level as endogenous opioid stimulated through exercise and it may have related to psychological and physiological condition.[44] Endorphinergic neurons certainly have a pivotal role in the brain's processing of painful stimuli. Pain sensation in many level in the central nervous system including spinal cord, midbrain, thalamus, and cortex was regulated by endorphin. The function of endorphin and pain sensation affected in affective inflammatory condition. Endorphinergic neurons play a fundamental role in selective attention, information of sensory in the somatosensory.[45] Experimental study in pregnant rats showed that the administration of narcotic antagonist naltrexone activated the endorphinergic neuron resulted to the endorphin secretion. The high level of endorphin increases the maternal pain threshold in pregnant rats.[46] In addition, the administration of capsaicin in chronic pain treatment can increase, fasten and ease the challenging path of managing pain sensation consequently that might improve the patient's quality of life.

Conclusions

The oral administration of capsaicin with respectively dose of 15mg, 30mg, 45mg can regulate the serum level of PGE2 and Endorphin after 24 hours of orthodontic tooth movement in Wistar Rats (*Rattus novergicus*). The oral administration of 15 mg Capsaicin can decrease significantly PGE2 serum level, while 30 mg of capsaicin administration can enhance significantly the level of endorphin serum level after 24 hours of orthodontic tooth movement *in vivo.* The further study needed to investigate the molecular pathway with various examination methods to confirm capsaicin regulate the PGE2 and endorphin serum level during OTM *in vivo.*

Declaration of Interest

The authors report no conflict of interest.

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