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Effects of various analgesics on the level of prostaglandin E2 during orthodontic tooth movement

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SUMMARY

AIM: The aim of this double-blind, randomized, placebo-controlled clinical study was to evaluate the analgesic effects of preoperative/postoperative ibuprofen and acetaminophen use after bonding and to find a relation between the pain level and the amount of prostaglandin released.

MATERIALS AND METHODS: Forty-eight patients were included and randomly divided to three equal groups that received either ibuprofen, acetaminophen or placebo for pain relief. The pain levels were measured before bonding, after bonding, at first, second, third, and seventh days on a 100 mm visual analogue scale (VAS) and gingival crevicular fluid (GCF) samples were collected at the same time intervals to measure the amount of prostaglandin E2 (PGE2) released. PGE2 levels were determined with ELISA test. The results were evaluated with Wilcoxon and Kruskal–Wallis tests with Bonferroni correction.

RESULTS: Acetaminophen and placebo groups showed similar pain levels during the first 2 days, whereas ibuprofen group showed lower pain levels during the first day after bonding. PGE2 levels did not show statistically significant difference in time within the analgesic groups. No significant relation between the pain perceived and PGE2 released was found.

LIMITATIONS: The biggest limitation of this study is the subjective nature of pain and its method of evaluation.

CONCLUSIONS: The perception of pain by patients taking ibuprofen and acetaminophen at pre/post appliance placement was not different from patients taking placebo. No time-related differences in PGE2 level were found between the groups and no significant correlation was found between the perception of pain and PGE2 levels.

Introduction

Orthodontic treatment is not painless, especially in the first weeks of appliance placement. Orthodontic literature is full of reports that mention about the negative effects of pain on the patients' daily activities after the placement of fixed appliances (Brown and Moerenhout, 1991; Sergl *et al.*, 1998). Therefore, pain caused by the orthodontic appliances remain to be an issue that need not be underestimated by the clinician.

Orthodontic pain is caused by the release of algogenic materials like prostaglandins (PG), histamin, bradykinin, and leukotrienes. Several pain control methods (Roth and Thrash, 1986; Fujiyama *et al.*, 2008; Hwang *et al.*, 1994) have been introduced and the most commonly used method still remains to be the pharmacological administration of analgesics. Non-steroidal anti-inflammatory drugs (NSAID) that block prostaglandin production are commonly given to patients for pain relief. The analgesic efficacy of different analgesics like aspirin, ibuprofen, flurbiprofen, naproxen sodium and acetaminophen have been tested for the control of orthodontic pain (Bernhardt *et al.*, 2001; Polat and Karaman, 2005; Bird *et al.*, 2007; Bradley *et al.*, 2007; Krishnan, 2007; Xiaoting *et al.*, 2010). However, these chemicals are also responsible for the initiation of the osteoclastic activity and therefore a delay in orthodontic tooth movement can be expected. Orthodontic literature is lacking information about the efficacy of different type of analgesics and their relevance to the release of prostaglandins. The purpose of this study is to find a relation between the analgesic efficacy of two types of analgesics, ibuprofen and acetaminophen, given both pre- and post-treatment and the level of prostaglandin E_2 (PGE2) released after initial archwire placement.

Materials and methods

This prospective, randomized, double-blind, placebo-controlled study was approved by the Baskent University Institutional Review Board and Ethics Committee. Sixty orthodontic patients who were scheduled to receive fixed orthodontic treatment agreed to participate in this study. A detailed medical history was taken for each patient. Both the parents and the patients were informed about the procedure, and an informed consent was obtained.

The following selection criteria were required for participation: 1. no prophylactic antibiotic coverage required, 2. no history of systemic diseases or allergies, 3. no current use of antibiotics or analgesics, 4. no contraindication to the use of NSAID, 5. no teeth extraction at least 4 weeks before bonding, 6. no history of orthodontic treatment, 7. not being in the menstrual period for female patients and 8. minimal crowding of maximum 7 mm that can be treated without extractions.

Proposed treatments were nonextraction but patients with open bites were excluded from the study. All of the patients received an education for maintaining the optimum oral hygiene and the patients with gingival problems were included to the study after periodontal therapy.

Randomization

The flow chart of the study is given in Figure 1. Forty-six patients were randomly allocated to one of three study groups in order. The groups were named as A, B, and C and both the patient and the investigator (ZT), who was responsible from the clinical part of the study, did not have any knowledge about the type of analgesic that were given to each group. The tablets were identical in shape and colour and did not have any markings or labels that represented brand name. The tablets were put in small pill boxes with a sticker containing the name of the group. The pills were put in the boxes by the second investigator, and the first investigator who coordinated the clinical part of the study did not have any knowledge about the grouping.

Study groups

Three experimental groups were predetermined: group A, 400 mg ibuprofen; group B, 500 mg acetaminophen; group C, lactose placebo capsule. In all groups, the patients took two tablets, one tablet an hour before the appointment and the other six hours after bonding. Patients were instructed not to take any additional analgesics.

In order to stimulate a routine clinical set-up, brackets were only placed to upper 10 teeth including the second promolars and first molars were banded. After the placement of upper appliances, 0.014 inch archwire was placed for levelling.

Pain assessment

Subjects were given routine post-treatment instructions and asked to complete a questionnaire at appropriate intervals during the week after the bonding appointment. The questionnaire was in the format of a six-page booklet that contained 100 mm horizontal visual analogue scales (VAS) on which the patient marked the degree of discomfort at the indicated time periods. The patients were instructed to make a check on the scale at each time interval to represent the perceived severity of pain during each of the three activities: chewing, fitting the front teeth, and fitting the back teeth. Incidence and severity of pain were recorded by the patient prior to bonding, right after the bonding, and on the first, second, third and seventh day after bonding. Patients were asked to return the questionnaire on the seventh day.

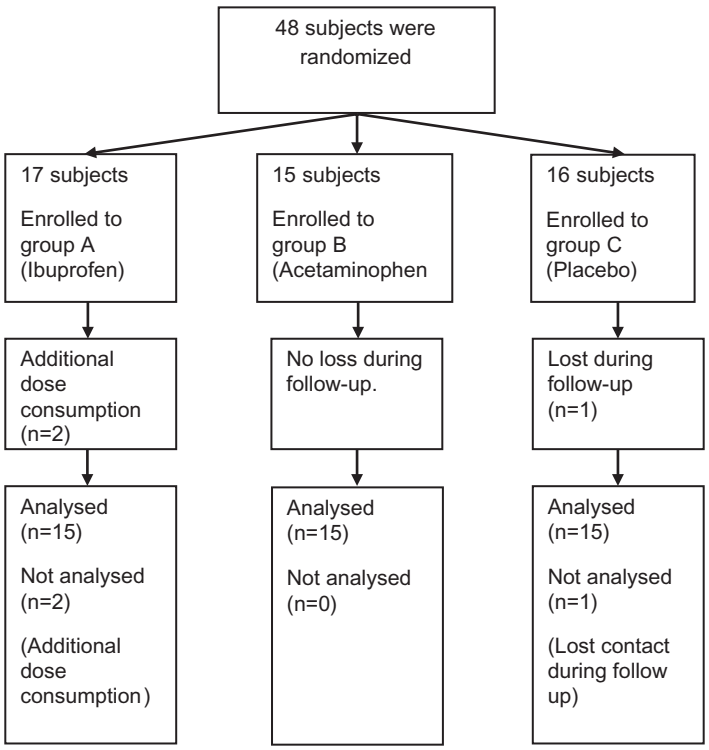

Figure 1 The flow chart of the study.

Gingival crevicular fluid collection

Gingival crevicular fluid (GCF) was collected by means of Periopaper (Oraflow, New York, USA) from the mesial and distobuccal sites of the two canines using a standardized method at each time interval. Briefly, each tooth included in the study was isolated with cotton rolls, and the tooth surface was dried gently with air. The strip was then inserted 1 mm into the sulcus and left *in situ* for 30 seconds. The amount of GCF was measured with Periotron 8000 (Oraflow, New York, USA). After collection, it was placed in Eppendorf tubes and immediately stored at −80 degree Celsius until the day for the ELISA test.

Determination of prostaglandin E2 levels

Prostaglandin E_2 EIA Kit–Monoclonal (Cayman Chemical Company, Ann Arbor, Michigan, USA) was used to evaluate the concentration of PGE2 in the collected GCF samples. This kit is based on the competition of PGE2 and PGE2–acetylcholinesterase complex (PGE2 tracer) for a certain amount of PGE2 monoclonal antibody. All tests for the determination of PGE2 levels were performed at Baskent University, Faculty of Medicine, Department of Microbiology.

The samples, which were stored in Eppendorf tubes prior to the analysis, were diluted with 75 µl/strip buffer solution, according to the manufacturer instructions. The samples were shaken at least 15 seconds in Vortex machine. After the placement of the samples into the wells (50 µl per well), PGE2 tracer and PGE2 monoclonal antibody were added in an amount of 50 µl into the wells. The test plate cover was closed and incubated at 4 degree Celsius for 18 hours. After incubation the plate was washed with the wash buffer for five times and Ellman's reagent was added in the wells. Then the plate was covered with a plastic membrane and incubated in an orbital shaker in the dark for 80 minutes. The colour density seen on the plate was read with ELx800 Universal Microplate Reader (BioTek Instruments, Vermont, USA). The density of the colour and the concentration of PGE2 were seemed to be inversely correlated. Standard curves were created for each kit and the concentration of PGE2 in the GCF was calculated with the implication of density values on these standard curves. PGE2 concentrations were found as pg/µl.

Statistical analysis

The statistical evaluation of the data was made by a professional statistical expert using SPSS for Windows 11.5 software (SPSS Inc., Chicago, Illinois, USA). The distribution of the VAS levels and PGE2 concentrations was checked using the Shapiro–Wilk Test. Descriptive statistics were shown with median (minimum–maximum) values. Age differences were evaluated using one way analysis of variance. All of the analyses were repeated for chewing, fitting back teeth, and fitting anterior teeth.

The differences in each drug group over time by means of pain and PGE2 values were evaluated using Wilcoxon test with Bonferroni correction. Since 45 multiple comparisons were made, a significance value of $P < 0.0011$ was considered significant.

The differences between the groups over time by means of pain and PGE2 values were evaluated using Kruskal–Wallis test with Bonferroni correction. Eighteen multiple comparisons were made and a significance value of $P < 0.003$ was considered significant.

Any possible relation between pain levels and PGE2 released at each time interval was checked using Spearman correlation analysis with Bonferroni Correction. A significance level of $P < 0.0011$ was preset.

Results

All of the 48 patients returned their forms back; however, two patients were excluded from the study for taking rescue medication and one patient for missing one of the GCF collection appointments. The average age at enrollment for the three groups was not significantly different from each other as shown in Table 1. Gender differences are not taken into consideration.

The pain levels of the groups after initial archwire placement

In all of the groups, the pain level peaked within 1 day after archwire placement. The average pain levels at Day 1 were similar for acetaminophen and placebo groups during chewing and fitting front teeth. The average pain reduction for the ibuprofen group was superior to both placebo and acetaminophen during chewing and fitting front teeth and

Table 1 Distribution of the study groups.

Group	Analgesic	Mean age	Minimum age	Maximum age	*F*	*P*	Girl	Boy
A	Ibuprofen	14.66±2.06	11.9	20.5			8	7
B	Acetaminophen	14.34±1.91	10.8	16.3	0.91	0.913	11	4
C	Placebo	14.50±2.16	11.5	19.7			12	3
Total		14.50±2.00	10.8	20.5			31	14

All the data are presented as mean (95% confidence interval).

the differences were statistically significant. ($P < 0.0011$; Table 2).

At Day 2, significant pain levels were measured for both acetaminophen and placebo groups during chewing. The pattern of pain was similar between the ibuprofen and the acetaminofen groups during fitting front teeth and fitting back teeth and only the placebo group reported significant pain during this functional activity at Day 2. ($P < 0.0011$; Table 2).

At Day 3, none of the analgesic groups reported significant pain levels but the placebo group still experienced significant amount of pain. ($P < 0.0011$) (Table 2).

Evaluation of PGE2 levels

In the placebo group the PGE2 levels were found as 22.33±17.21 pg/µl, 16.81 ± 11.69 pg/µl, 17.33 ± 13.53 pg/µl, 21.37 ± 24.33 pg/µl, 17.66 ± 14.90 pg/µl, 16.18 ± 10.08 pg/µl at the predetermined time intervals, respectively. The difference was not significant in all time intervals. ($P < 0.0011$).

In the ibuprofen group, the mean PGE2 levels were measured as 14.53 ± 13.27 pg/µl, 9.27 ± 4.81 pg/µl, 19.30 ± 17.25 pg/µl, 14.52 ± 13.78 pg/µl, 9.96 ± 7.16 pg/µl, 11.59 ± 11.84 pg/µl and the mean PGE2 levels for the acetaminophen group were 16.14 ± 12.59 pg/µl, 10.89 ± 10.53 pg/µl, 16.66 ± 14.39 pg/µl, 21.78 ± 40.11 pg/µl, 14.63 ± 11.35 pg/µl, 15.91 ± 13.705 pg/µl, respectively. For these two analgesic groups, the mean PGE2 levels in time were also insignificant ($P < 0.0011$) (Table 3).

The mean PGE2 levels of the analgesic groups were lower than placebo in some time intervals but the differences were not statistically significant. ($P > 0.003$).

Correlation between pain and PGE2 levels

No associations were found between the PGE2 levels and the intensity of pain at any time interval. However, since the correlation analyses are mostly dependent on the number of subjects, the ibuprofen and acetaminophen groups were merged and re-evaluated to increase the strength of the analysis. Nevertheless no significant difference was found between the intensity of pain and PGE2 levels ($P > 0.05$; Table 4)

Discussion

Pain and discomfort are one of the most common complaints of orthodontic patients, especially on the first week

Table 2 The pain levels of the three groups at measured function and time intervals.

	Ibuprofen	Acetaminophen	Placebo	*P*
Chewing				
Before bonding	0.00 (0–0)	0.00 (0–0)*,**	0.00 (0–0)*,**,*******	
After bonding	0.00 (0–6,7)	0,00 (0–4.3)***,****	0.34 (0–5.6)****,********	0.769
Day 1	4.67 (0–10)	6.36 (1.5–1.0)*,***,*****	7.40 (0–9.3)*,*****	0.146
Day 2	5.40 (0–10)	5.30 (0–10)**,****,******	7.16 (2.8–9.7)**,****,******	0.030
Day 3	2.90 (0–8.5)	2.81 (0–9.7)	6.25 (1.5–10.0)*******,********,*********	0.027
Day 7	0.74 (0–7.0)	0.45 (0–2.5)*****,******	0.00 (0–6.0)*****,******,*********	0.831
Fitting front teeth				
Before bonding	0.00 (0–0.9)	0.00 (0–1)*	0.00 (0–0)*,***,****	
After bonding	0.00 (0–4.1)	0.00 (0–4.3)**	0.0 (0–5.3)**,*****,******	0.564
Day 1	2.69 (0–10.0)	6.34 (0–10)*,**	6.05 (2.8–9.4)*,**	0.524
Day 2	5.00 (0–10)	4.79 (0–10)	6.58 (2.6–10.0)***,*****,*******	0.157
Day 3	2.85 (0–9.4)	2.43 (0–9.4)	5.18 (1.0–10.0)****,******,********	0.203
Day 7	0.85 (0–7.8)	0.50 (0–8.4)	0.64 (0–6.2)*******,********	0.603
Fitting back teeth				
Before Bonding	0.00 (0–3.5)	0.00 (0–0)	0.00 (0–0)*,**	
After bonding	0.80 (0–6.6)	0.00 (0–6.5)	0.47 (0–6.4)***	0.712
Day 1	5.30 (0–10)	5.13 (0–9.1)	7.11 (0–10)	0.235
Day 2	5.28 (0–10)	4.04 (0–9.2)	6.68 (3.8–9.7)*,***,****	0.030
Day 3	2.23 (0–8.5)	2.82 (0–8.7)	6.17 (1.9–10.0)**,*****	0.015
Day 7	0.90 (0–6.6)	0.00 (0–2.4)	0.00 (0–4.8)****,*****	0.652

*Significant differences were detected between before bonding and Day 1 ($P < 0.0011$); **Significant differences were detected between after bonding and Day 1 ($P < 0.0011$); ***Significant differences were detected between before bonding and Day 2 ($P < 0.0011$); ****Significant differences were detected between before bonding and Day 3 ($P < 0.0011$); *****Significant differences were detected between after bonding and Day 2 ($P < 0.0011$); ******Significant differences were detected between after bonding and Day 3 ($P < 0.0011$); *******Significant differences were detected between Day 2 and Day 7($P < 0.0011$); ********Significant differences were detected between Day 3 and Day 7 ($P < 0.0011$).

Table 3 Distribution of PGE2 concentrations in the groups in time.

Follow-up	Ibuprofen	Acetaminophen	Placebo	*P*
After initial archwire	−1.16 (−18.52–50.29)	0 (−23.75–33.14)	−5.85 (−37.27–27.51)	0.879
Day 1	0 (−8.20–19.82)	0 (−30.12–142.55)	−1.18 (−34.32–53.41)	0.486
Day 2	−6.23 (−41.03–20.16)	0 (−28.01 – 22.43)	−1.8 (−47.61–8.96)	0.863
Day 3	−1.6 (−26.29–14.89)	0 (−32.68 – 40.43)	−6.04 (−42.75–11.42)	0.522
Day 7	−2.79 (−32.06–11.14)	−3.06 (−27.11–7.79)	−6.98 (−28.37–28.80)	0.792

A confidence value of $P < 0.0011$ was determined after Bonferroni correction.

Table 4 Correlation coefficients between PGE2 levels and pain.

Groups		After IA	Day 1	Day 2	Day 3	Day 7
Ibuprofen	Correlation coefficient (*P*)	−0.398 (0.142)	−0.313 (0.256)	0.158 (0.575)	−0.040 (0.888)	−0.056 (0.842)
Acetaminophen	Correlation coefficient (*P*)	0.04 (0.887)	0.47 (0.077)	0.538 (0.039)	0.285 (0.303)	0.147 (0.601)
Placebo	Correlation coefficient (*P*)	−0.128 (0.649)	0.114 (0.685)	0.043 (0.879)	−0.036 (0.899)	−0.294 (0.287)
Ibuprofen + Acetaminophen	Correlation coefficient (*P*)	−0.198 (0.295)	−0.142 (0.454)	0.136 (0.473)	0.14 (0.462)	−0.112 (0.555)

A confidence value of $P < 0.0011$ was determined after Bonferroni correction.

of fixed appliance placement. The severity of pain derived from orthodontic appliances vary greatly by age, type of force, and personality type (Salmassian *et al.*, 2009) and even the appliance acceptance of patients after 6 months could be predicted from their attitude toward treatment and the amount of discomfort experienced (Doll *et al.*, 2000). With such an importance on patient compliance and comfort, pain control and management should be a priority for the clinician.

Tooth movement is a complex phenomenon. According to the pressure-tension theory, tooth movement occurs in three stages: obstruction in blood flow after the application of pressure to the periodontal ligament (PDL), release of chemical messengers, and activation of bone resorption (Sandy and Harris, 1984; Reitan and Rygh, 2007). Prostaglandin E2 and interleukin-1 β, which are important for the cellular response in the initiation of bone resorption, are released in the PDL and the GCF within a short time after the application of pressure and mediators such as prostaglandin E2 and interleukin-1β are involved in the mediation of orthodontic pain (Celebi *et al.*, 2013). NSAIDS, which are commonly given to patients for pain relief, block PG production. Acetaminophen, unlike NSAIDS, is inactive as an anti-inflammatory agent in peripheral tissues and does not prevent PG synthesis and tooth movement. The aims of this study were to assess the efficacy of ibuprofen and acetaminophen administered before or after orthodontic activation with regard to pain control and PGE2 levels and to find possible associations between PGE2 released in GCF and the intensity of pain.

Pain is a subjective sensation and of multifactorial origin. Several methods were proposed for pain assessment in the literature and almost all of them rely on subjective recordings. Verbal rating scales, behavioural rating scales, and numeric scales are the commonly used methods (Polat, 2007). Like most of the studies in orthodontic literature, a VAS was used for pain assessment in this study. Although it does not provide an objective recording, VAS was found superior to other pain scales in terms of reproducibility and ease of measurement (Dubner, 1978; Seymour *et al.*, 1985).

When previous studies on analgesic efficiancy of ibuprofen, acetaminophen and placebo on orthodontic pain were reviewed, conflicting results were seen. Bernhardt *et al.* (2001) found that patients who took both preoperatively and/or postoperatively administrated ibuprofen felt less pain than other analgesics. Bradley *et al.* (2007) have found less pain in their ibuprofen group compared to acetaminophen. One of the latest studies on orthodontic pain has also shown that acetaminophen and placebo have similar analgesic activity, whereas ibuprofen had significant effects on lowering orthodontically induced pain (Patel *et al.*, 2011). However Bird *et al.* (2007) have shown that similar results were seen between acetaminophen and ibuprofen after the placement of separators on molar teeth. Similarly, Salmassian *et al.* (2009) have found no differences between the two drugs. In a systematic review that was published recently, it was shown that no statistical differences were detected between placebo, ibuprofen or acetaminophen (Xiaoting *et al.*, 2010). The results of the present study also could not show differences in pain levels of patients taking

placebo, ibuprofen or acetaminophen. Some possible reasons were questioned for this result. First of all, only two doses were administrated for this study, which may be inadequate to detect statistically significant differences. Doses of 400 mg ibuprofen and 600 mg acetaminophen were shown to be superior to placebo for dental pain but some investigators advised orthodontic patients to use regular doses for the first week of appliance placement (Salmassian *et al.*, 2009; Bradley *et al.*, 2007; Polat *et al.*, 2005). One other possible reason can be the strong psychological effect of placebo drugs, which should not be underestimated. The present study model was a double-blind, placebo-controlled study and therefore the effect of the placebo could be obtained at a higher level. It was shown by Bouncher (1999) in medical and dental studies that the placebo effects could be as high as 30–40 per cent. In a previous study by Bartlett *et al.* (2005), it was shown that even a structured telephone call asking about how the patients felt in the first week after bonding, significantly lowered pain levels.

Different inflammatory mediators like PGE2, IL-1β, IL-6 and substance P is released during orthodontic tooth movement. In a canine retraction model, the levels of PGE2 and IL-1β showed rapid increases in the first 24 hours of appliance placement and returned to baseline levels after the first week compared with the contralateral control group (Grieve *et al.*, 1994). In a different study that used the same model, the efficacy of aspirin and rofecoxib was investigated on PGE2 concentrations in GCF (Sari *et al.*, 2004). It was shown that both of the drugs lowered PGE2 levels on the first and second day of appliance placement, whereas PGE2 levels of placebo group showed a significant rise only on the first day and did not change for the rest of the week. Contrary to these results, in premolar extraction patients, IL-1β and TNF-α did not show significant differences during levelling in Day 7 and 21, but showed a rapid rise on sixth month when 150 g force was applied for canine distalization (Başaran *et al.*, 2006). The results of this study did not find significant differences in PGE2 levels with acetaminophen, ibuprofen, and placebo. The study model of this group was not an extraction model. Only nonextraction patients were included and evaluations were made only on the first week of levelling. According to Başaran *et al.*, PGE2 levels reached a significant level only during canine distalization and not during levelling. In a study where the effect of light (50 g) and heavy (150 g) forces of the release of IL-1β, it was shown that the changes were not significant on the first hour, first day and first week in group where light force was applied (Luppanapornlarp *et al.*, 2010). Therefore, the similarities between the groups of the current study could be attributed to the low levels of force during levelling. However, the results of these studies should be interpreted with caution. It was assumed that the repeatability of GCF collection and quantification procedures show large variations, which may indicate large intersubject and intrasubject errors (Perinetti *et al.*, 2013). In a study by Perinetti *et al.* (2013), no systematic error was found but the method error (i.e. intrasubject variability) ranged from 40 to 58 per cent for overall gingival fluid. Ongoing controversy also exist in using PGE2 level or concentrations and so far no consensus have been reached.

Only two studies are present in the orthodontic literature that try to find a relation between the perception of pain and the level of inflammatory mediators (Sari *et al.*, 2004; Giannopoulou *et al.*, 2006). Giannopoulou *et al.* (2006), tried to find a correlation between pain levels and IL-1β, PGE2 and substance P levels at first hour, first and seventh days after elastic separator placement. Their results revealed no significant correlation between PGE2 levels and pain but significant correlation between IL-1β and pain levels was detected on the first day. In another study, IL-1β, PGE2 and substance P levels in pressure and tension regions were investigated and significant differences were detected in pressure region (Sari *et al.*, 2004). In the present study, no specific pressure or tension regions are present, which would explain the differences with our results and the current literature.

Orthodontic tooth movement is not controlled by only one chemical mediator. It is a multifactorial process and 1–2 day analgesic use during the most painful first week of fixed appliance placement seems not to interfere with future tooth movement (Giannopoulou *et al.*, 2006; Polat, 2007; Ngan *et al.*, 1994). However, in patients with chronic illnesses like juvenile rheumatoid arthritis, osteoarthritis or gout, where long-term analgesic consumption is needed, special attention should be given.

Conclusions

1. The perception of pain by patients taking ibuprofen and acetaminophen at pre- or post-appliance placement was not different from patients taking placebo.
2. No time-related differences in PGE2 level were found between the groups.
3. No significant correlation was found between the perception of pain and PGE2 levels.

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