Original Article

Effects of Preoperative Ibuprofen and Naproxen Sodium on Orthodontic Pain

Omur Polat[a]; Ali Ihya Karaman[b]; Ercan Durmus[c]

Abstract: Three experimental groups of 20 patients each, all of whom were to undergo fixed orthodontic treatment, were enrolled in this prospective study. Group 1 was given a placebo, group 2 was given 400 mg ibuprofen, and group 3 was given 550 mg naproxen sodium. All the patients received only one dose that was given one hour before archwire placement. All patients were asked to complete a questionnaire concerning the pain perceived after archwire placement. The questionnaire was in the form of a seven-page booklet that contained 100-mm horizontal Visual Analogue Scale 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 four activities, ie, chewing, biting, fitting back teeth together, and fitting front teeth together. Incidence and severity of pain were recorded by the patient at two hours, six hours, nighttime on the day of appointment, 24 hours after the appointment, and two days, three days, and seven days after bonding. The results revealed that patients taking 550 mg naproxen sodium one hour before archwire placement had significantly lower levels of pain at two hours, six hours, and nighttime after adjustment than patients taking placebo or ibuprofen. However, the use of additional postoperative doses was recommended to control orthodontic pain completely. (*Angle Orthod* 2005;75:791–796.)

Key Words: NSAID; Ibuprofen; Naproxen sodium; Orthodontic pain

INTRODUCTION

Pressure delivered to a tooth by orthodontic appliances results in ischemia, inflammation, and edema immediately after the compression of the periodontal ligament.[1] Algogens such as histamine, bradykinin, prostaglandins, serotonin, and substance P are released after periodontal ligament compression and activation of the inflammatory reaction.[2] Pain during orthodontic treatment usually appears at two hours after application of orthodontic force, reaches a peak level at 24 hours, and lasts approximately five days.[3–6]

Pain is of multifactorial nature and depends on variables such as patient's subjective previous pain experiences, age, type of appliance, present emotional state and stress, cultural differences, and sex.[7] Studies evaluating the nature of pain felt after oral surgery procedures have reported possible sex differences in the degree of pain response.[2,8] However, the situation is different for the orthodontic patient in that clinicians have not agreed on sex differences in the degree of pain felt by the orthodontic patient.[9–11] Possible sex differences in orthodontic pain response are thought to be related to culture rather than to physiological factors.[7]

Discomfort and pain after initial seperator or archwire placement are common experiences among orthodontic patients. It is one of the main reasons that discourages patients from seeking orthodontic treatment.[12] Pain during orthodontic treatment may have a negative influence on cooperation, and some patients may even stop brushing their teeth due to pain. In a study that consisted of 203 Chinese orthodontic patients, 91% of them reported pain caused by fixed orthodontic appliances and 39% reported pain during every visit.[13] Kvam et al[14] in Norway and Scheurer et al[15] in Switzerland reported that 95% of orthodontic patients experienced varying degrees of discomfort during treatment.

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Accepted: May 2004. Submitted: April 2004.

Different methods have been developed to control pain during orthodontic treatment including the application of low-level laser therapy to periodontal tissues,[16] transcutaneous electrical nerve stimulation (TENS),[17,18] and vibratory stimulation of the periodontal ligament.[19] To some degree these have been tried, and pain control has been achieved. However, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is the preferred method of pain control related to fixed orthodontic appliances. Anti-inflammatory drugs such as aspirin and ibuprofen have been evaluated in the previously literature.[3,5,6,20] Ngan et al[3] made the first studies on analgesics and evaluated the analgesic efficacy of ibuprofen and aspirin on 77 patients in a placebo-controlled, double-blind, single-dose study. They found that the placebo group felt more pain than the patients who had received either ibuprofen or aspirin. They also reported that patients who received ibuprofen after seperator or archwire insertion felt less pain than patients who received aspirin.

Recently much attention has been paid to preoperative analgesic consumption in both the medical and dental literature. Preoperative analgesic consumption provides the blockage of afferent nerve impulses before they reach the central nervous system. If NSAIDs are given before the procedure, the body absorbs them before tissue damage and subsequent prostaglandin production. It was reported previously that NSAID application before oral surgery decreases the pain intensity and delays both the onset and peak pain levels.[20,21] In orthodontic literature, Law et al[5] and Bernhart et al[6] have evaluated the efficacy of preoperative analgesic consumption and both have found that ibuprofen taken one hour before archwire or band application decreases the pain levels from two hours after bonding until nighttime.

Only the efficacy of aspirin and ibuprofen has been studied so far in orthodontic literature. Naproxen sodium is a propionic acid derivate like ibuprofen, and its analgesic effect is comparable to ibuprofen.[2] However, the duration of action of naproxen is longer than ibuprofen.[2] The recommended schedule of administration is 500 mg initially, followed by 250 mg doses at 8- to 12-hour intervals.[2] The aim of this study is to evaluate the efficacy of preoperative administration of ibuprofen and naproxen sodium on orthodontic pain after archwire placement.

MATERIALS AND METHODS

Subjects

Sixty orthodontic patients who were scheduled to receive fixed orthodontic treatment agreed to participate in this study. The following selection criteria were required for participation: no prophylactic antibiotic coverage required; no systemic diseases; currently not using antibiotics or analgesics; no contraindication to the use of NSAID; a minimum weight requirement based on Food and Drug Administration–approved over-the-counter pediatric dosage labeling guidelines; no teeth extracted at least two weeks before bonding.

A detailed medical history was taken for each patient, and any patient with a history of a systemic disease was excluded from the study. Both the parents and the patients were informed about the procedure, and an informed consent was obtained.

Twenty patients were randomly assigned to each of three experimental groups, ie, group A, lactose capsule; group B, 400 mg ibuprofen; and group C, 550 mg naproxen sodium. In all groups, patients took only one tablet, one hour before archwire placement. The patient and research assistant were blinded to each subject's experimental group.

Subjects were given routine posttreatment instructions and were asked to complete a questionnaire at appropriate intervals during the week after the bonding appointment. The questionnaire was in the format of a seven-page booklet that contained 100-mm horizontal Visual Analogue Scale (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/discomfort during each of four activities that included chewing, biting, fitting back teeth, and fitting front teeth. The incidence and severity of pain were recorded by the patient at two hours, six hours, bedtime on the day of appointment, 24 hours after the appointment, and two days, three days, and seven days after bonding. Patients were asked to return the questionnaire at the next appointment.

Patients were instructed not to take any additional analgesics. If additional ''rescue'' medication was needed, they were instructed to indicate the date and the dosage of the medication taken. All the patients returned their questionnaires, and none of them had taken any additional analgesics.

Statistics

All the statistical analyses were made using the Statistical Package for Social Sciences 10.0 (SPSS Inc, Chicago, Ill). Descriptive statistics were calculated for pain scores at each time interval for the experimental groups. Analysis of variance (ANOVA) was used to find the differences in age among the groups.

Comparisons between the three experimental groups in four parameters were made using repeated measures two-way ANOVA. If the results of repeated measures ANOVA were found significant, one-way ANOVA was carried out for each time interval, and

TABLE 1. Groups With Mean Age and Sex Distribution

Group No.	Preoperative Analgesic	Preoperative Dose	Mean Age	No. of Boys	No. of Girls
1	Placebo	1 tablet	16 ± 6.1	10	10
2	Ibuprofen	400 mg	17 ± 7.0	13	7
3	Naproxen sodium	550 mg	15 ± 2.2	14	6

TABLE 2. Mean Pain Scores and Standard Deviations of the Experimental Groups[a]

Groups	2 h	6 h	At night	24 h	2 d	3 d	7 d
Chewing							
Placebo	3.81 ± 3.28	5.19 ± 3.31	5.99 ± 2.89	5.94 ± 3.12	4.23 ± 2.8	3.27 ± 2.81	1.43 ± 1.81
Ibuprofen	2.18 ± 2.68	3.49 ± 3.04	4.96 ± 3.97	5.46 ± 3.82	5.01 ± 3.10	4.94 ± 3.07	1.55 ± 2.49
Naproxen sodium	1.43 ± 2.66	1.62 ± 2.40	2.81 ± 2.76	3.41 ± 3.27	3.60 ± 3.16	2.48 ± 3.09	0.36 ± 1.12
Biting							
Placebo	3.91 ± 3.42	6.05 ± 3.27	6.61 ± 2.92	6.66 ± 2.96	5.15 ± 3.03	4.76 ± 2.97	2.81 ± 2.21
Ibuprofen	2.15 ± 2.44	4.56 ± 3.50	5.08 ± 3.56	6.08 ± 3.38	5.54 ± 2.83	4.38 ± 3.03	1.79 ± 2.54
Naproxen sodium	2.54 ± 3.15	4.86 ± 2.02	5.11 ± 3.20	5.11 ± 3.20	5.53 ± 3.22	4.69 ± 3.29	0.89 ± 1.67
Fitting front teeth							
Placebo	3.91 ± 3.42	6.05 ± 3.27	6.61 ± 2.92	6.66 ± 2.96	5.15 ± 3.03	4.76 ± 2.97	2.81 ± 2.21
Ibuprofen	2.03 ± 2.52	4.09 ± 3.69	5.68 ± 3.66	6.27 ± 2.75	6.24 ± 3.34	4.88 ± 3.62	4.88 ± 3.62
Naproxen sodium	1.39 ± 2.72	2.75 ± 2.89	4.03 ± 2.76	5.32 ± 2.81	6.30 ± 3.10	5.30 ± 3.97	1.68 ± 2.72
Fitting back teeth							
Placebo	3.33 ± 3.01	5.20 ± 3.35	5.38 ± 3.20	5.17 ± 3.29	3.39 ± 3.03	2.22 ± 2.21	1.49 ± 2.04
Ibuprofen	2.20 ± 2.19	2.21 ± 2.19	3.50 ± 3.41	4.90 ± 3.92	3.76 ± 3.38	3.34 ± 3.21	1.22 ± 2.38
Naproxen sodium	1.16 ± 2.59	1.19 ± 2.29	2.08 ± 2.78	2.95 ± 2.93	3.41 ± 2.81	2.42 ± 3.47	0.70 ± 2.24

[a] Values are mean ± SD.

multiple comparisons were made with Tukey HSD test. In this study, level of significance for repeated measures ANOVA and Tukey test was determined as $P < .05$.

RESULTS

The descriptive statistics for the three experimental groups are given in Table 1. As a result of ANOVA, the mean ages of the subjects were similar between the three experimental groups ($P < .05$). Depending on the previous studies that revealed no differences in pain response between girls and boys, the findings were evaluated without sex discrimination.

According to the results of repeated measures ANOVA, there were significant relationships between drug groups and time in chewing, biting, fitting front teeth together, and fitting back teeth together ($P < .05$). The mean pain values and standard deviations for chewing, biting, fitting front teeth together, and fitting back teeth together in each of the three experimental groups are shown in Table 2.

Differences in postoperative pain between experimental conditions

The one-way ANOVA to compare the differences between the experimental groups at each time intervals showed significant differences in ''pain to chewing'' at two hours, at six hours, and at the night after bonding ($P < .05$). The results of Tukey test revealed significant differences between the placebo group and naproxen sodium group at two hours, six hours, and at night ($P < .05$). There was no significant difference in pain levels between groups at any subsequent postoperative times (Figure 1).

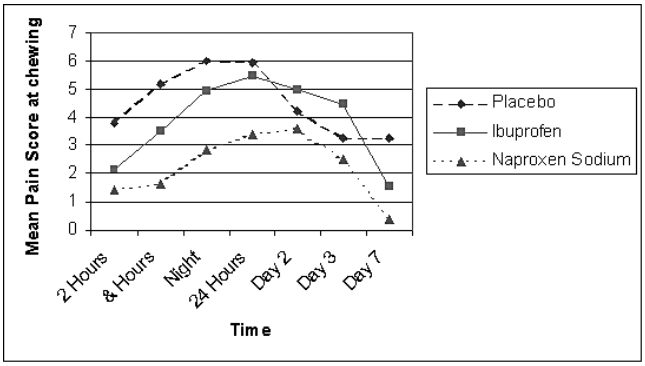

FIGURE 1. Mean pain scores for ''chewing,'' by condition and time.

For ''pain to biting,'' significant differences were observed only at two hours and six hours ($P < .05$). At these two time intervals, patients who took naproxen sodium one hour before archwire placement felt less

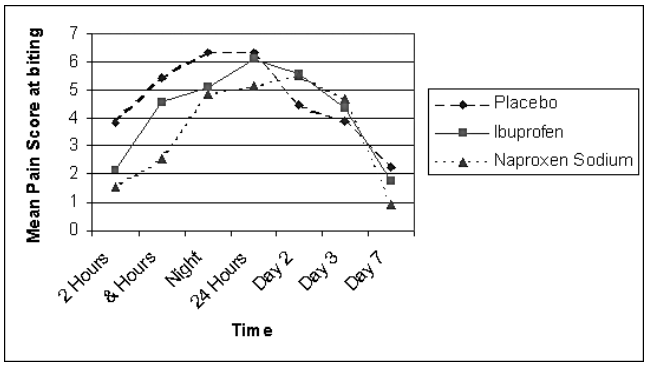

FIGURE 2. Mean pain scores for ''biting,'' by condition and time.

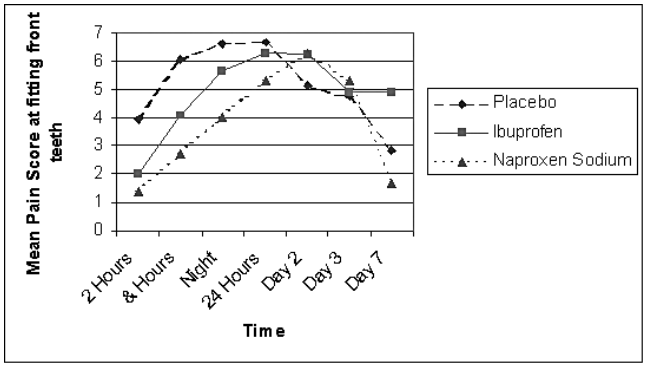

FIGURE 3. Mean pain scores for ''fitting front teeth together,'' by condition and time.

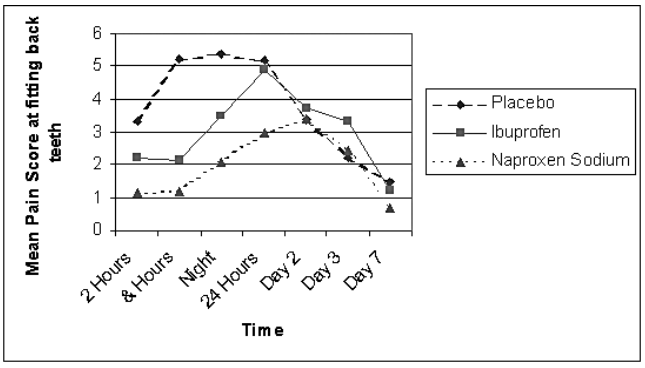

FIGURE 4. Mean pain scores for ''fitting back teeth together,'' by condition and time.

pain than patients taking both placebo and ibuprofen ($P < .05$) (Figure 2).

There were significant differences at two hours, six hours, and at nighttime in ''pain when fitting front teeth together'' (Figure 3) and ''pain when fitting back teeth together'' (Figure 4) ($P < .05$). The naproxen sodium group felt less pain than both placebo and ibuprofen groups in all these measurements. No significant differences were measured between the placebo and ibuprofen groups at these time intervals ($P > .05$).

DISCUSSION

This study was performed on 60 patients who were to undergo fixed orthodontic treatment. Three experimental groups included group 1, placebo; group 2, 400 mg ibuprofen; and group 3, 550 mg naproxen sodium. All the patients received only one dose that was given one hour before archwire placement.

The patients were asked to complete a questionnaire concerning the pain perceived after archwire placement. The questionnaire was in the form of a seven-page booklet that contained 100-mm horizontal VAS on which the patient marked the degree of pain/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 four functional activities of chewing, biting, fitting back teeth together, and fitting front teeth together. The incidence and severity of pain were recorded by the patient at two hours, six hours, nighttime on the day of appointment, 24 hours after the appointment, and two days, three days and seven days after bonding.

Sex discrimination was not included because of previous results that had shown no correlation between pain and sex.[9–11] Patients with similar ages, malocclusions, and social class were selected for this study.[3]

Because no method exists to measure a pain response objectively, we used a 100-mm VAS, which was shown to be a reliable and easy subjective method of measuring pain intensity.[7]

The results of this study reveal that patients who took naproxen sodium preoperatively had significantly less pain than patients who took placebo or ibuprofen while chewing, fitting front teeth, and fitting back teeth at two hours, six hours, and nighttime after archwire placement. The results of pain to biting were found to be quite similar, except that there were no differences in pain scores between the three experimental groups at nighttime. Jackson et al[20] and Dionne and Cooper[21] had previously found that NSAIDs taken before oral surgery procedures could delay the onset and severity of pain. The probable mechanism for preoperative anti-inflammatory effect is the blockage of prostaglandin synthesis in peripheral tissue. If NSAIDs were given before the procedure, the body absorbs them before prostaglandin production, and this decreases the inflammatory response. According to the results of the present study, when compared with the placebo group, the preoperative use of both ibuprofen and naproxen sodium decreased the pain levels at two hours and six hours after archwire placement, but the results were statistically significant for the naproxen sodium group only.

The studies that investigated the effects of preop-

erative analgesic administration before archwire placement so far have investigated only the effects of ibuprofen.[5,6] Law et al[5] found that preemptive ibuprofen significantly decreased pain to chewing at two hours compared with postoperative ibuprofen or placebo. Similar to that, Bernhart et al[6] found decreased pain scores in patients taking pre- or postoperative ibuprofen compared with patients taking only postoperative ibuprofen.

The results of this study found no significant differences in pain responses between the placebo and ibuprofen groups. However, patients who took naproxen sodium one hour before archwire placement had decreased levels of pain. The disagreement with the findings of these two studies and the present study for the analgesic effect of ibuprofen is probably because of the multifactorial nature of pain. Individual pain response depends on variables such as the patient's subjective previous pain experiences, age, type of appliance, present emotional state and stress, cultural differences.[7]

Peak pain had occurred at night or 24 hours after archwire adjustment, and pain levels of the patients who agreed to participate in this study started to decrease at 24 hours after archwire placement. Naproxen sodium is a long-acting NSAID with analgesic activity requiring only twice a day dosage, and its effect has been studied in oral surgery.[2] Single doses of 220 mg of naproxen and 200 mg of ibuprofen were comparable in onset of analgesic action and in pain relief but with prolonged duration of action of naproxen. In this study, naproxen sodium was found effective to reduce pain in pain to chewing, ''pain to fitting front teeth,'' and ''pain to fitting back teeth'' at two hour, six hours, and at nighttime after archwire placement. The analgesic activity of naproxen sodium was not sufficient in pain to biting even at the night after the adjustment. Therefore, it is recommended that in addition to one preoperative dose, at least one more postoperative analgesic tablet, preferably two, should be given to the orthodontic patient for pain control.

Gastric or duodenal ulceration, bleeding disorders, renal insufficiency, asthma, and allergy, hypertension, congestive heart problems, atherosclerosis, and interaction with antihypertension drugs are among the common adverse effects seen with NSAIDs.[2] Kehoe et al[22] found that ibuprofen significantly inhibited the production of prostaglandin E (PGE) in the periodontal ligament and, subsequently, decreased the rate of tooth movement.

On the other hand, although the acetaminophen had an inhibitory effect on peripheral prostaglandin (PGE) synthesis at the level of the periodontal ligament, the rate of tooth movement was not significantly different from the controls. They concluded that acetaminophen is the analgesic of choice for the relief of orthodontic discomfort. Walker and Buring[23] reported that NSAIDs inhibit the cyclooxygenase pathway and therefore the production of PGE, and it was thought that NSAIDs may inhibit the osteoclastic activity necessary for tooth movement and slow the rate of orthodontic tooth movement. The dosage of the anti-inflammatory drugs used in these studies was much higher than over-the-counter therapeutic doses. In clinical orthodontics, lower doses are used for a short duration (1–3 days) after orthodontic activation. In a healthy patient without any systemic diseases, these doses are eliminated from the body before orthodontic tooth movement is started.

There is no standard care for analgesic usage to relieve pain caused by fixed orthodontic appliances. This study aimed to evaluate the analgesic effect of ibuprofen and naproxen sodium, and naproxen sodium was found to have superior analgesic activity compared with both ibuprofen and placebo. However, before reaching a final conclusion, several other studies evaluating the efficacy of safer and longer-acting NSAIDs are needed.

CONCLUSIONS

The results demonstrated that

- Naproxen sodium (550 mg) taken one hour before archwire placement significantly decreased the severity of pain at two hours, six hours, and, except for pain to biting, 24 hours when compared with preoperatively administrated ibuprofen (400 mg) or placebo.
- As maximum pain levels were felt on the night to 24 hours after archwire adjustment, a single dose of an analgesic given preoperatively was found insufficient to relieve pain; therefore, at least one additional postoperative dose is recommended.

REFERENCES

1. Furstman L, Bernik S. Clinical considerations of the periodontium. *Am J Orthod.* 1972;61:138–155.
2. Skjelbred P, Lökken P. Pain and other sequelae after surgery-mechanisms and management. In: Andreasen JO, Petersen JK, Laskin DM, eds. *Textbook and Color Atlas of Tooth Impactionsy*. Copenhagen: Munksgaard; 1997:369–437.
3. Ngan PW, Wilson S, Shanfeld J, Amini H. The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *Am J Orthod Dentofac Orthop.* 1994; 106:88–95.
4. Wilson S, Ngan P, Kess B. Time course of the discomfort in patients undergoing orthodontic treatment. *Pediatr Dent.* 1989;11:107–110.
5. Law SLS, Southard KS, Law AS, Logan HL, Jakobsen JR. An evaluation of postoperative ibuprofen treatment of pain associated with orthodontic separator placement. *Am J Orthod Dentofac Orthop.* 2000;118:629–635.

6. Bernhart MK, Southhard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. *Am J Orthod Dentofac Orthop.* 2001;120:20–27.
7. Bergius M, Kiliaridis S, Berggren U. Pain in orthodontics. *J Orofac Orthop.* 2000;61:125–137.
8. Feinmann C, Ong M, Harwey W, Harris M. Psychological factors influencing post-operative pain and analgesic consumption. *Br J Oral Maxillofac Surg.* 1987;25:285–292.
9. Ngan P, Bratford K, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment. *Am J Orthod Dentofac Orthop.* 1989;96:47–53.
10. Jones M, Chan C. The pain and discomfort experienced during orthodontic treatment. A randomised controlled trial of two aligning archwires. *Am J Orthod Dentofac Orthop.* 1992;102:373–381.
11. Erdinc AME, Dincer B. Perception of pain during orthodontic treatment with fixed appliances. *Eur J Orthod.* 2004;26:79–85.
12. Oliver R, Knapman Y. Attitudes to orthodontic treatment. *Br J Orthod.* 1985;12:179–188.
13. Lew KK. Attitudes and perception of adults towards orthodontic treatment in an Asian community. *Community Dent Oral Epidemiol.* 1993;21:31–35.
14. Kvam E, Bondevik O, Gjerdet NR. Traumatic ulcers and pain during orthodontic treatment. *Community Dent Oral Epidemiol.* 1989;17:154–157.
15. Scheurer P, Firestone A, Bürgin W. Perception of pain as a result of orthodontic treatment with fixed appliances. *Eur J Orthod.* 1996;18:349–357.
16. Lim HM, Lew KKK, Tay DKL. A clinical investigation of the efficacy of low level laser therapy in reducing orthodontic postadjustment pain. *Am J Orthod Dentofac Orthop.* 1995; 108:614–622.
17. Roth PM, Thrash WJ. Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. *Am J Orthod Dentofac Orthop.* 1986;90:132–138.
18. Weiss DD, Carver DM. Transcutaneous electrical neural stimulation for pain control. *J Clin Orthod.* 1994;28:670–671.
19. Marie SS, Powers M, Sheridan JJ. Vibratory stimulation as a method of reducing pain after orthodontic appliance adjustment. *J Clin Orthod.* 2003;37:205–208.
20. Jackson D, Moore P, Hargreaves K. Postoperative nonsteroidal anti-inflammatory medication for the prevention of postoperative dental pain. *J Am Dent Assoc.* 1989;119:641–647.
21. Dionne RA, Cooper S. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. *Oral Surg Oral Pathol Oral Radiol Endod.* 1978;45:851–856.
22. Kehoe MJ, Cohen SM, Zarrinnia K, Cowan A. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. *Angle Orthod.* 1996;66:339–350.
23. Walker JB, Buring SM. NSAID impairment of tooth movement. *Ann Pharmacother* 2001;35:113–115.

Original Article

TMJ Osteoarthritis/Osteoarthrosis and Immune System Factors in a Japanese Sample

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ABSTRACT

Objective: To determine whether there is an association between temporomandibular joint (TMJ) osteoarthritis/osteoarthrosis (OA) and immune system factors in a Japanese sample.

Materials and Methods: The records of 41 subjects (7 men, aged 22.0 ± 3.8 years; 34 women, aged 24.8 ± 6.3 years) and 41 pair-matched controls (7 men, aged 22.1 ± 2.3 years; 34 women, aged 24.8 ± 6.4 years) based on age and gender were reviewed. Information on medical history included local or systemic diseases, details on medication type and use, and the presence of allergies and asthma. Dental history questions referred to details regarding past oral injuries. The validity of the hypothesis, defining allergies and asthma as risk factors in OA, was tested by using a logistic regression analysis.

Results: The incidence of allergy was significantly higher in the TMJ OA ($P = .008$), with a mean odds ratio of 4.125 and a 95% confidence interval of 1.446–11.769.

Conclusion: These results suggest that allergy may be a risk factor in association with TMJ OA in this Japanese sample.

KEY WORDS: TMJ OA; Risk factors; Allergy; Asthma

INTRODUCTION

Arthritis refers to inflammation of the articular surfaces of a joint. Osteoarthritis (OA) is one of the most common forms of arthritis affecting the temporomandibular joint (TMJ) and has been referred to as a degenerative joint disease.[1]

Although the precise causes of OA are unknown, its most common etiologic factor is generally thought to be overloading of the articular structures of the joint.[2–4] When bony changes are active, the condition is often painful. When the actual cause of OA can be identified, the condition is referred to as secondary osteoarthritis. On the other hand, when the cause cannot be determined, it is referred to as primary osteoarthritis.[1] In either case, as functional remodeling occurs, the condition becomes stable, although the bony changes still remain. This condition is referred to as osteoarthrosis and is nature's way of adapting to the functional demands of the system.[1] Radiographic changes are commonly detected in osteoarthritis/osteoarthrosis.

The TMJ is believed to be in a constant state of remodeling (cellular and extracellular matrix turnover).[5] The primary goal of remodeling is to maintain functional and mechanical relationships between articulating surfaces of the joint. Remodeling is an essential biological response to normal functional demands, ensuring homeostasis of joint form and function and an optimal occlusal relationship between the two dental arches. In addition, remodeling may take place when changes occur either in the adaptive capacity of the host or when mechanical stresses are placed on the joint structures. Host factors (ie, age, systemic dis-

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Accepted: November 2007. Submitted: September 2007.

ease, hormones) may contribute to dysfunctional remodeling of the TMJ, even when the biomechanical stresses are within a normal physiological range.[6,7] Alternatively, excessive mechanical stress may provoke dysfunctional remodeling in the absence of predisposing host factors.[5,6] The exact molecular mechanisms of degenerative TMJ disease, however, are unknown. Three mechanisms (direct mechanical injury, hypoxia-reperfusion injury, and neurogenic inflammation) of injury have been suggested.[6] All of these changes can lead to a net loss of tissue by increasing degradation processes (catabolic) and inhibiting synthetic processes (anabolic) in affected articular tissues.

Neurogenic inflammation has been cited as a possibly mediating condylar morphologic change.[8] Traction or compression of peripheral nerve terminals in the joint may evoke a release of neuropeptides (substance P, calcitonin gene-related peptide [CGRP]) into the surrounding tissues. These neuropeptides are vasoactive. When mechanically strained, these neuropeptides are released from nerve endings adjacent to blood vessels, causing local hypotension, leading to plasma extravasation and migration of leukocytes out of capillaries. These migratory cells initiate an inflammatory reaction, typified by the synthesis and secretion of chemokines, cytokines, growth factors, and colony-stimulating factors. These signal molecules attract osteoclast and osteoblast progenitor cells to the affected area, thus sustaining the inflammatory process. In this fashion, inflammation governs the remodeling of the TMJ. In addition, inflammatory cytokines can increase the synthesis of these neuropeptides in a positive feedback mechanism.[9–11] Therefore, the inflammatory process produced by the stimulation of peripheral nerve terminals in the TMJ can lead to a self-perpetuating cycle. Consequently, the presence of primed leukocytes in the peripheral blood, which originate in diseased organs such as lungs and joints, supports the notion of a possible association between TMJ OA and pathological conditions that affect and/or involve the immune system.

It has been reported that immune system factors are associated with excessive dental root resorption[12–14] and excessive alveolar bone resorption.[15,16] However, no report exists regarding the relationship between TMJ OA and immune system factors. In lieu of the reports linking signal molecules derived from immune cells with enhanced root resorption and bone remodeling in mechanically loaded dental and paradental tissues, we hypothesize that individuals who have medical conditions that affect the immune system, such as allergies and asthma, may be at a high level of risk for TMJ OA. The objective of this study was to determine whether there is an association between TMJ OA and the presence of systemic diseases that affect the immune system in a Japanese sample.

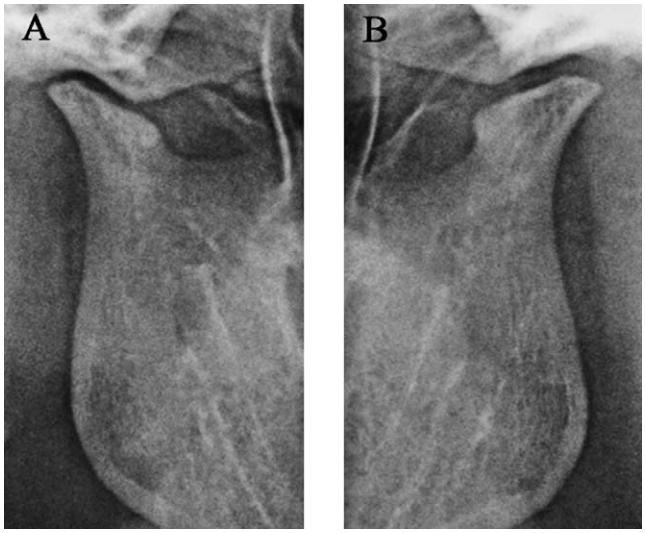

Figure 1. Examples of temporomandibular joint (TMJ) osteoarthritis. (A) Right side of TMJ. (B) Left side of TMJ.

MATERIALS AND METHODS

This study was a retrospective analysis of existing radiographs and was performed in accordance with the guidelines of the Helsinki Declaration (1996).

The sample was selected from the case files of the Department of Orthodontics, Faculty of Dentistry, Kyushu University, Fukuoka, Japan, which included more than 2000 documented individual records. These records contained a pretreatment questionnaire, medical history, and pretreatment dental panoramic and transcranial radiographs. The questionnaire included the documentation of TMJ pain, TMJ sounds, and mandibular restriction of mouth opening.

Determination of the TMJ OA status of each patient was established by an examination of the pretreatment radiographs. Individuals aged 16 years or older were assigned to the TMJ OA group when bilateral condylar bony changes (flattening, osteophyte, and erosion) were detected. The radiographs were interpreted by an experienced radiologist, who implemented the TMJ OA definitions and scoring system published by Muir and Goss.[17] We determined scores of 1 and 2 corresponding to mild bony change and gross bony change, respectively, as constituting TMJ OA (Figure 1). Eighteen cases, in which radiographic interpretation was ambiguous, and two rheumatoid arthritis cases were excluded from this study.

In this population, 41 individuals were found to have bilateral TMJ OA. In this group, 7 subjects were male (aged 22.0 $\pm$ 3.8 years) and 34 were female (aged 24.8 $\pm$ 6.3 years). A control group was selected from

Table 1. Comparison of Means and Standard Deviations of Age in the TMJ OA and Control Groups[a]

	No. of Subjects	Age, y
TMJ OA group		
Male	7	22.0 ± 3.8
Female	34	24.8 ± 6.3
Total	41	24.3 ± 6.0
Control group		
Male	7	22.1 ± 2.3
Female	34	24.8 ± 6.4
Total	41	24.5 ± 6.0

[a] TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthrosis.

the remaining patients of this population who did not display bilateral radiographic evidence of TMJ OA. Each individual in the control group was pair matched to another in the TMJ OA group based on age and gender. In the control group, 7 subjects were male (aged 22.1 ± 2.3 years) and 34 were female (aged 24.8 ± 6.4 years; Table 1). Student's *t*-tests were used to compare the mean difference in age between the TMJ OA and the control groups. No significant difference in the mean age was found between the two groups.

Subjects or their legal guardians recorded answers to a questionnaire prior to the onset of treatment. The questionnaire sought information on personal demographics, medical history, and dental history. Information in the medical history included local or systemic diseases (ie, bone disorders, heart disease, blood disease, liver disease, kidney disease, and respiratory disease), details on medication type and use, the presence of allergies (ie, allergic rhinitis, allergic urinary, allergic response to food or metal, pollen allergy, and atopic dermatitis) and asthma. Dental history questions referred to details regarding previous dental treatment and information about past oral injuries.

Statistical Analysis

The validity of our hypothesis was tested by the logistic regression analysis using the Stat View 5.0 program (SAS Institute Inc, Cary, NC). This analysis is a variation of ordinary regression, applicable when the observed outcome is restricted to two values, which represent the occurrence or nonoccurrence of an outcome event (TMJ OA). It produces a formula that predicts the probability of the occurrence as a function of the independent variables. Logistic regression also produces odds ratios associated with each predictor variable (trauma, allergy, asthma, systemic disease, medication use). The result is the odds of an event occurring divided by the probability of the event not occurring.

Table 2. Prevalence of Subjective TMJ Pain and TMJ Sounds in the TMJ OA and Control Groups[a]

	TMJ OA Group	Control Group
TMJ pain, %	34.1	5.9
TMJ sounds, %	70.7	19.5

[a] TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthrosis.

RESULTS

The prevalence of the subjective signs and symptoms of TMJ dysfunction in TMJ OA and control groups is shown Table 2. The prevalence of bilateral TMJ OA was 2.1%. The distribution of each risk factor in the TMJ OA and control groups is shown in Table 3. The logistic regression analysis is shown in Table 4. The incidence of allergy was significantly higher in the TMJ OA group ($P = .008$), with a mean odds ratio of 4.125 and 95% confidence interval of 1.446–11.769. The incidences of the other factors were not significant between the two groups.

DISCUSSION

TMJ OA, which is a degenerative disease common to human general joints, is defined for the TMJ as deterioration of the articular cartilage layer with structure changes of subchondral bone. Factors that influence the host remodeling capacity of the TMJ may include advancing age and hormonal factors.[7] It is reported that progressive resorption occurred in a young age group (second and third decade).[18–21] Occurrence at this age is secondary to reduced host adaptive capacity and diminished cellular density in the articular cartilages.[22,23] Furthermore, females are more likely to be afflicted with OA than males are.[24,25] Females might be predisposed to dysfunctional remodeling of the TMJ, and this female preponderance for dysfunctional remodeling of the TMJ suggested a potential role of sex hormones (ie, estrogen, prolactin) as modulators of this response.[18] Based on that premise, in this study, each individual in the control group was pair matched

Table 3. Distribution for Each Risk Factor in the TMJ OA and Control Groups

	TMJ OA Group			Control Group		
Risk Factor	Male	Female	Total	Male	Female	Total
Trauma	1	3	4	2	3	5
Allergy	3	16	19	2	5	7
Asthma	0	4	4	1	2	3
Systemic disease	1	7	8	1	2	3
Medication use	0	5	5	0	2	2

[a] TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthrosis.

Table 4. Logistic Regression Analysis of Each Risk Factor

Risk Factor	χ^2	*P* Value	Odds Ratio	95% Confidence Interval
Trauma	0.530	.818	0.840	0.189–3.722
Allergy	7.020	.008	4.125	1.446–11.769
Asthma	0.246	.620	1.551	0.274–8.771
Systemic disease	1.933	.164	2.635	0.672–10.325
Medication use	0.670	.413	2.164	0.341–13.744

to another in the TMJ OA group based on age and gender.

TMJ OA still bristles with unclear points regarding the involved cellular and tissue mechanisms underlying this pathological process. However, one biological pathway of TMJ OA has been identified as neurogenic inflammation.[5,6] Traction or compression of the nerve-rich regions of the TMJ may result in the release of neuropeptides from the peripheral terminals into the affected tissue. Some neuropeptides, such as substance P and CGRP, may stimulate the production and release of proinflammatory cytokines (ie, interleukin-1 [IL-1], tumor necrosis factor [TNF]) by local cell populations.[26–30] These cytokines may in turn stimulate the production, release, and/or activation of the matrix degrading enzyme as well as activate both phospholipase A_2 and cyclooxygenase, leading to the production of prostaglandins and leukotrienes. Prostaglandins, such as PGE_2, may sensitize peripheral nerve terminals in the region, leading to a continued release of proinflammatory neuropeptides. This interaction may potentially lead to a self-perpetuating cycle that can amplify the inflammatory response. In this disease state, the delicate balance between catabolic and anabolic events is perturbed, resulting in a net loss of articular tissue. Furthermore, the levels of several cytokines, including IL-1β, IL-6, TNF-α, IL-8, and interferon-γ, were reported to be increased in synovial fluid samples taken from patients with temporomandibular disorders, and these cytokines may play a role in the pathogenesis of synovitis and degenerative changes of the cartilaginous tissue and bone of the TMJ.[31] Therefore, it is reasonable to hypothesize that patients with local or systemic diseases that involve the immune system may be susceptible to TMJ OA because at least some of their circulating leukocytes are primed to produce high levels of inflammatory mediators and growth factors.

Allergy is associated with a set of abnormal genetically regulated immune responses to a variety of allergens. Allergic individuals are characterized by the excessive production of IgE, antibodies to the allergens, and many major classes of cytokines, which have been organized into different categories according to their major functional activities.[32]

In this study, we found that allergy might be an etiological factor in TMJ OA. Our finding supports the hypothesis that allergies may be high-risk factors for TMJ OA. Similarly, we hypothesized that asthma might be one of the high-risk factors in TMJ OA because circulating lymphocytes from asthma patients produce large amounts of interleukins 2, 4, and 5.[33] However, we did not find a significant association between the two pathologies. This statistical finding does not preclude the existence of an association between asthma and TMJ OA because only a few patients with asthma were included in our sample (four patients with asthma in the TMJ OA group; three patients with asthma in the control group). Therefore, additional research on a larger sample appears to be warranted.

One limitation of this study was that determination of the TMJ OA status of each patient was established by examination of dental panoramic radiographs. It has been suggested that bony tissues are best imaged with computed tomography (CT) scan.[34] The greatest advantage of the CT scan is that it images both hard and soft tissue.[35] However, the disadvantages of the CT scan are that it is time consuming, expensive, and a procedure with high radiation exposure.

Although there is a controversy regarding the utility of the dental panoramic radiographic imaging in both general practice and when evaluating the TMJ,[36] the panoramic and transcranial radiographs have been widely used in dental offices, providing useful diagnostic images for screening purposes.[37] The accuracy of determining bony changes by using panoramic radiographs was reported to be from 71% to 84%.[38,39] Therefore, the validity and impact of the results should be interpreted with caution.

In this study, the subjects were grouped into the TMJ OA group when the bilateral bony changes (flattening, osteophyte, and erosion) were obvious in the panoramic and transcranial radiographs according to the definitions and scoring system published by Muir and Goss.[17] Recently, it was reported that cone beam CT is one of the best choices for imaging diagnosis of the TMJ OA.[40] Cone beam CT, which reproduces multiple images, including axial, coronal, and sagittal planes of the joint, provides a complete radiographic investigation of the bony components of the TMJ. However, these images were not available to us at the time of this investigation.

CONCLUSION

- Allergy may be a risk factor in association with TMJ OA in this Japanese sample. However, the small size of our sample precluded the exposure of additional physiological and medical conditions that may

contribute, alone or in concert with other factors, to the etiology of TMJ OA.

REFERENCES

1. Okeson JP. *Management of Temporomandibular Disorders and Occlusion.* 4th ed. St Louis, Mo: Mosby; 1998.
2. Stegenga B, de Bont LG, Boering G, et al. Tissue responses to degenerative changes in the temporomandibular joint: a review. *J Oral Maxillofac Surg.* 1991;49:1079–1088.
3. de Bont LG, Stenaga B. Pathology of temporomandibular joint internal derangement and osteoarthrosis. *J Oral Maxillofac Surg.* 1993;22:71–74.
4. Pereira FJ Jr, Lundh H, Westesson PL. Morphologic changes in the temporomandibular joint in different age groups: an autopsy investigation. *Oral Surg Oral Med Oral Pathol.* 1994;78:279–287.
5. Arnett GW, Milam SB, Gottesman L. Progressive mandibular retrusion—idiopathic condylar resorption: part I. *Am J Orthod Dentofacial Orthop.* 1996;110:8–15.
6. Milam SB, Schmitz JP. Molecular biology of temporomandibular joint disorders: proposed mechanisms of disease. *J Oral Maxillofac Surg.* 1995;53:1448–1454.
7. Moffett BC, Johnson LC, McCabe JB, et al. Articular remodeling in the adult human temporomandibular joint. *Am J Anat.* 1964;115:119–142.
8. Kido MA, Kiyoshima T, Kondo T, et al. Distribution of substance P and calcitonin gene-related peptide-like immunoreactive nerve fibers in rat temporomandibular joint. *J Dent Res.* 1993;72:592–598.
9. Cavagnaro J, Lewis RM. Bidirectional regulatory circuit between the immune and neuroendocrine systems. *Year Immunol.* 1989;4:241–252.
10. Jonakait GM, Schotland S. Conditioned medium from activated splenocytes increases substance P in synthetic ganglia. *J Neurosci Res.* 1990;26:24–30.
11. Eskay RL, Eiden LE. Interleukin-1 alpha and tumor necrosis factor-alpha differentially regulate enkephalin, vasoactive intestinal polypeptide, neurotensin, and substance P biosynthesis in chromaffin cells. *Endocrinology.* 1992;130:2252–2258.
12. Nishioka M, Ioi H, Nakata S, Nakasima A, Counts A. Root resorption and immune system factors in the Japanese. *Angle Orthod.* 2006;76:103–108.
13. Davidovitch Z, Lee YJ, Counts AL, et al. The immune system possibly modulates orthodontic root resorption. In: Davidovitch Z, Mah J, eds. *Biological Mechanisms of Tooth Movement and Craniofacial Adaptation.* Boston, Mass: Harvard Society for the Advancement of Orthodontics; 2000: 207–217.
14. Owman-Moll P, Kurol J. Root resorption after orthodontic treatment in high- and low-risk patients: analysis of allergy as a possible predisposing factor. *Eur J Orthod.* 2000;22: 657–663.
15. Taubman MA, Valverde P, Han X, et al. Immune response: the key to bone resorption in periodontal disease. *J Periodontol.* 2005;76:2033–2041.
16. Persson GR. What has ageing to do with periodontal health and disease? *Int Dent J.* 2006;56:240–249.
17. Muir GB, Goss AN. The radiographic morphology of asymptomatic temporomandibular joints. *Oral Surg Oral Med Oral Pathol.* 1990;70:349–354.
18. Arnett GW, Tamborello JA. Progressive Class II development—female idiopathic condylar resorption. In: West RA, ed. *Oral Maxillofacial Clinics of North America.* Philadelphia, Pa: WB Saunders; 1990:699–716.
19. Susami T, Kuroda T, Yano Y, Nakamura T. Growth changes and orthodontic treatment in a patient with condylolysis. *Am J Orthod Dentofacial Orthop.* 1992;102:295–301.
20. Rabey GP. Bilateral mandibular condylysis—a morphanalytic diagnosis. *Br J Oral Surg.* 1977–1978;15:121–134.
21. Kirk WS. Failure of surgical orthodontics due to temporomandibular joint internal derangement and postsurgical condylar resorption. *Am J Orthod.* 1992;101:375–380.
22. Livne E, Weiss A, Silbermann M. Articular chondrocytes lose their proliferative activity with aging yet can be resimulated by PTH(-1-84), PGE1, and dexamethasone. *J Bone Miner Res.* 1989;4:539–548.
23. Silbermann M, Livne E. Age-related degenerative changes in the mouse mandibular joint. *J Anat.* 1979;129:507–520.
24. Blackwood HJJ. Arthritis of the temporomandibular joint. *Br Dent J.* 1963;115:317–326.
25. Toller PA. Osteoarthrosis of the mandibular condyle. *Br Dent J.* 1973;134:223–231.
26. Basbaum AI, Levine JD. The contribution of the nervous system to inflammation and inflammatory disease. *Can J Physiol Pharmacol.* 1991;69:647–651.
27. Yaksh TL. Substance P release from knee joint afferent terminals: modulation by opioids. *Brain Res.* 1988;458:319–324.
28. Lotz M, Vaughan JH, Carson DA. Effect of neuropeptides on production of inflammatory cytokines by human monocytes. *Science.* 1988;241:1218–1221.
29. Laurenzi MA, Persson MA, Dalsgaard CJ, et al. The neuropeptide substance P stimulates production of interleukin 1 in human blood monocytes: activated cells are preferentially influenced by the neuropeptide. *Scand J Immunol.* 1990;31:529–533.
30. Said SI. Neuropeptides as modulators of injury and inflammation. *Life Sci.* 1990;47:19–21.
31. Takahashi T, Kondou T, Fukuda M, et al. Proinflammatory cytokines detectable in synovial fluids from patients with temporomandibular disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85:135–141.
32. Bellanti JA. Cytokines and allergic diseases: clinical aspects. *Allergy Asthma Proc.* 1998;19:337–341.
33. Walker C, Bode E, Boer L, et al. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis.* 1992;146:500–506.
34. Brooks SL, Brand JW, Gibbs SJ, et al. Imaging of the temporomandibular joint: a position paper of the American Academy of Oral and Maxillofacial Radiology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;83:609–618.
35. Westesson PL, Katzberg RW, Tallents RH, et al. CT and MR of the temporomandibular joint: comparison with autopsy specimens. *Am J Roentgenol.* 1987;148:1165–1171.
36. Epstein JB, Galdwell J, Black G. The utility of panoramic imaging of the temporomandibular joint in patients with temporomandibular disorders. *Oral Surg Oral Med Oral Pathol.* 2001;92:236–239.
37. Kononen M, Kilpinen E. Comparison of three radiographic methods in screening of temporomandibular joint involvement in patients with psoriatic arthritis. *Acta Odontol Scand.* 1990;48:271–277.
38. Kobayashi K, Kondoh T, Sawai K, et al. Image diagnosis for internal derangements of the temporomandibular joint: the advantages and limitations of imaging techniques. *Oral Radiol.* 1991;7:13–24.
39. Kakudo K. The significance and problems of the rotational

panoramic radiography as routine screening tests for osteoarthritis of the temporomandibular joint. *J Jpn Assoc Dent Sci.* 1995;14:43–47.
40. Meng JH, Zhang WL, Liu DG, et al. Diagnostic evaluation of the temporomandibular joint osteoarthritis using cone beam computed tomography compared with conventional radiographic technology. *Beijing Da Xue Xue Bao.* 2007;39: 26–29.

Erratum

Vol. 75, No. 5, September 2005, page 793.

''Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain''.
Omar Polat, Ali Ihya Karaman and Ercan Durmus.
Angle Orthod. 2005;75:791–796.

TABLE 1. Groups With Mean Age and Sex Distribution

Group No.	Preoperative Analgesic	Preoperative Dose	Mean Age	No. of Boys	No. of Girls
1	Placebo	1 tablet	**16.15 ± 5.7**	10	10
2	Ibuprofen	400 mg	17 ± 7.0	13	7
3	Naproxen sodium	550 mg	15 ± 2.2	14	6

TABLE 2. Mean Pain Scores and Standard Deviations of the Experimental Groups[a]

Groups	2 h	6 h	At night	24 h	2 d	3 d	7 d
Chewing							
Placebo	**3.92 ± 3.18**	**5.18 ± 3.07**	**5.99 ± 2.88**	**4.47 ± 2.97**	**3.27 ± 2.81**	**3.27 ± 2.81**	**1.06 ± 0.80**
Ibuprofen	2.18 ± 2.68	3.49 ± 3.04	4.96 ± 3.97	5.46 ± 3.82	5.01 ± 3.10	4.94 ± 3.07	1.55 ± 2.49
Naproxen sodium	1.43 ± 2.66	1.62 ± 2.40	2.81 ± 2.76	3.41 ± 3.27	3.60 ± 3.16	2.48 ± 3.09	0.36 ± 1.12
Biting							
Placebo	**5.41 ± 2.78**	**5.73 ± 3.71**	**6.34 ± 2.93**	**6.69 ± 2.84**	**4.49 ± 1.95**	**3.78 ± 2.95**	**1.93 ± 1.72**
Ibuprofen	2.15 ± 2.44	4.56 ± 3.50	5.08 ± 3.56	6.08 ± 3.38	5.54 ± 2.83	4.38 ± 3.03	1.79 ± 2.54
Naproxen sodium	2.54 ± 3.15	4.86 ± 2.02	5.11 ± 3.20	5.11 ± 3.20	5.53 ± 3.22	4.69 ± 3.29	0.89 ± 1.67
Fitting front teeth							
Placebo	**3.81 ± 3.03**	**5.83 ± 3.13**	**6.55 ± 2.84**	**6.63 ± 2.91**	**5.11 ± 2.88**	**4.58 ± 2.87**	**2.57 ± 1.97**
Ibuprofen	2.03 ± 2.52	4.09 ± 3.69	5.68 ± 3.66	6.27 ± 2.75	6.24 ± 3.34	4.88 ± 3.62	4.88 ± 3.62
Naproxen sodium	1.39 ± 2.72	2.75 ± 2.89	4.03 ± 2.76	5.32 ± 2.81	6.30 ± 3.10	5.30 ± 3.97	1.68 ± 2.72
Fitting back teeth							
Placebo	**3.41 ± 3.01**	**5.20 ± 3.07**	**5.34 ± 3.07**	**5.22 ± 3.32**	**3.44 ± 2.97**	**2.24 ± 2.09**	**1.44 ± 1.46**
Ibuprofen	2.20 ± 2.19	2.21 ± 2.19	3.50 ± 3.41	4.90 ± 3.92	3.76 ± 3.38	3.34 ± 3.21	1.22 ± 2.38
Naproxen sodium	1.16 ± 2.59	1.19 ± 2.29	2.08 ± 2.78	2.95 ± 2.93	3.41 ± 2.81	2.42 ± 3.47	0.70 ± 2.24

[a] Values are mean ± SD.