Comparison of chewing gum and ibuprofen in alleviating orthodontic pain: a single centre, randomised clinical trial

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Background: The aim of the present three-arm parallel trial was to compare the effectiveness of chewing gum and ibuprofen in the control of orthodontic pain.

Methods: Patients to undergo orthodontic treatment at a private orthodontic clinic were randomly divided into three parallel groups, each of which took either a placebo, ibuprofen or chewing gum. The eligibility criteria included patients in the full permanent dentition with moderate crowding requiring the extraction of two mandibular and two maxillary premolars. The main outcome was the patient’s level of discomfort, which was assessed by a 0–10 numeric rating scale (NRS) at two hours, six hours, at bedtime, 24 hours, two days, three days and seven days after the placement of initial arch wires in four functions including chewing, biting, occluding back teeth, and occluding front teeth. Randomisation was accomplished according to the patient’s clinic entrance number and by using a table of random numbers. The patients in the placebo and ibuprofen groups were blinded to the type of medication used. The differences in the groups were analysed using repeated measures ANOVA.

Results: Sixty-six patients between 12 and 30 years were randomised in a 1:1:1 ratio. The pain questionnaire response rate was 100% in the three groups, but six patients were excluded and consequently 60 patients were analysed (N = 20 in each group). There was no significant difference between the chewing gum and ibuprofen groups during any oral function at any time point (p > 0.05). However, repeated measures ANOVA showed that patients in the placebo group experienced significantly higher pain scores compared with patients in the ibuprofen and chewing gum groups at two hours, six hours, at bedtime, at 24 hours and two days after initial arch wire placement (p < 0.05). No patient harm was observed in this study.

Conclusions: In contrast to the common orthodontic belief that gum chewing may lead to bracket breakage, it seems that chewing gum is as beneficial as medication for pain relief and can be a recommended alternative during orthodontic treatment. [Aust Orthod J 2020; 36: 38-44]

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Introduction

Pain from appliances is common during orthodontic treatment, and the fear of pain is a key reason why patients may avoid seeking care.1 Approximately 90 to 95% of patients report some level of discomfort during appliance treatment.2-4 Pressure applied to a tooth by orthodontic forces results in an inflammatory response within the periodontal ligament (PDL), which subsequently stimulates the release of mediators and generates pain and discomfort.5,6 Pain is usually felt within a few hours following force application and reaches a maximum intensity at 24 hours, after which the pain gradually subsides and disappears after five to seven days.1,4,7-10
Various methods have been suggested to control pain throughout appliance treatment. The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen that disrupts prostaglandin metabolism, is the most common method of pain management. However, the potential side effects of NSAIDs, such as gastrointestinal disorders, and the inhibition of prostaglandin synthesis that also decreases the rate of tooth movement are concerning, particularly in young patients.

Because of the concerns, non-medication methods of pain control, such as low-level laser therapy, transcutaneous electrical nerve stimulation and chewing gum or chewing on a bite wafer have been advocated. The mechanism of action of these methods is to loosen the tightly grouped fibres around the nerves and blood vessels in the PDL and to restore normal vascular and lymphatic circulation. This results in the prevention or resolution of inflammation and oedema and subsequently heralds a reduction in pain and discomfort. However, the effectiveness of chewing gum and its protocol for use in the relief of orthodontic pain have not been widely investigated compared with other methods, likely because of the fear that chewing gum may increase the incidence of bracket breakage. The present study was therefore designed to assess the efficacy of chewing gum to control orthodontic pain compared with ibuprofen and a placebo to establish a management guideline.

Methods

The present study was approved by the Ethics Committee of the Kerman University of Medical Sciences (No. KA/92/477) and conducted in a private orthodontic clinic. Informed consent was obtained from all patients who participated in this study.

**The inclusion criteria identified:**

a. Patients in the full permanent dentition.

b. Patients requiring full upper and lower fixed orthodontic treatment with no additional appliance (i.e., trans-palatal arch, headgear or elastics).

c. Patients with no active periodontal disease or history of previous orthodontic treatment.

d. Patients with no medical or mental problems.

e. Patients with moderate crowding (4–8 mm) in both arches.

f. Patients requiring the extraction of two maxillary and two mandibular premolars for orthodontic purposes.

Sixty-six patients between 12 and 30 years of age participated in the study. The subjects were randomly divided into three parallel groups in a 1:1:1 ratio according to their clinic admission number and by using a table of random numbers. Tooth extraction was performed at least two weeks prior to the placement of orthodontic appliances. Orthodontic separating elastics were placed one week prior to banding. All patients received bands on their first molars, 0.022 × 0.028 inch MBT brackets (Ortho Organizers, USA) and 0.014 inch NiTi initial arch wires (G&H, USA) in one appointment. The method of ligation was standardised by the complete engagement of the arch wires on all teeth using elastomeric ligatures. Patients in the placebo group received vitamin B6 (40 mg; DarouPakhsh Co., Tehran, Iran) for pain relief. Patients in the ibuprofen group received ibuprofen (400mg; DarouPakhsh Co., Tehran, Iran). The patients in these two groups were blinded to the type of ingested drug and were asked to take a tablet immediately after arch wire placement and at eight-hourly intervals for one week if the pain persisted. Patients in the third group chewed sugar-free gum (Trident, TX, USA) for 10 minutes immediately after arch wire placement and at eight-hourly intervals for one week if the pain continued.

The patient’s level of discomfort was assessed using a 0–10 numeric rating scale (NRS) at two hours, six hours, at bedtime after arch wire placement and at 24 hours, two days, three days, and seven days after the first appointment. The NRS used 0–10 integers to indicate the level of pain on a horizontal, 10 cm line comprising two endpoints; 0 indicated no pain while 10 indicated unbearable pain. All patients received an NRS questionnaire in the form of a seven-page booklet for noting the seven recording times. Each page contained four 10 cm NRSs for each function and patients were given oral instructions on how to complete the NRS questionnaire. The patients were asked to determine the level of pain experienced at the appropriate time points by marking the integers on the scale line. The severity of pain was expressed and experienced during four oral functions including chewing, biting, occluding the posterior teeth, and occluding the anterior teeth. To determine the biting
and chewing effects, patients were asked to bite or chew on a slice of apple and score the level of pain experienced. For occluding of the anterior and posterior teeth, the patients were asked to bite the front teeth edge-to-edge with a light force, to secondly occlude the posterior teeth with a light force, and then to record the level of pain experienced. The patients were instructed not to take any other analgesic medications in addition to those being used during the trial until the questionnaire was completed.

The normal distribution of variables was confirmed by the Kolmogorov-Smirnov test. The differences between the groups relevant to pain scores were analysed by repeated measures ANOVA and Tukey’s test. SPSS software (version 19; SPSS, IL, USA) was used for statistical analysis, and the level of significance for all tests was set at \( p < 0.05 \).

**Results**

Sixty-six patients between 12 and 30 years of age were randomised in 1:1:1 ratio to either the placebo, ibuprofen or the chewing gum group. No patient was lost to follow-up, but three patients took additional analgesics and three patients filled out the questionnaire incompletely (Figure 1). The study began in May 2014 and ended in February 2015.

![Figure 1. CONSORT diagram showing the flow of participants through each stage of the trial.](image-url)
Table I shows the demographic characteristics of the patients and indicates that the three groups were not significantly different in age and gender characteristics ($p > 0.05$).

The pain questionnaire response rate was 100% in the three groups, but six patients were excluded from the analysis because of additional analgesic intake or an incomplete questionnaire. Consequently, only 60 patients were analysed ($N = 20$ in each group). Table II shows the mean pain score for the different functions at the various time points in the three groups. The pattern of pain reported over time was almost similar for the three groups as pain reached its maximum intensity at 24 hours after arch wire placement (Table II). The differences in pain scores are presented individually for each function.

### Differences in pain scores on ‘chewing’

The result of ANOVA demonstrated that patients in the placebo group experienced significantly higher pain scores compared with patients in the ibuprofen and chewing gum groups at two hours, six hours, at bedtime, 24 hours and two days after initial arch wire placement ($p < 0.05$) (Table II). The maximum pain experienced was reported in the placebo group at 24 hours after initial arch wire placement; minimum pain pertained to the ibuprofen group at two hours (mean: 2.55; 95% CI: 1.22 to 3.88) after initial arch wire placement.

### Differences in pain scores on ‘biting’

With respect to pain experienced on biting, patients in the ibuprofen and chewing gum groups showed significantly less pain than the placebo group at two hours, six hours, bedtime and 24 hours after initial arch wire placement ($p < 0.05$) (Table II). However, the chewing gum group did not show any significant difference in pain score compared with the ibuprofen group at any time point ($p > 0.05$). Maximum pain was experienced by the placebo group (mean: 7.65; 95% CI: 6.5 to 8.7) at 24 hours after initial arch wire placement while minimum pain pertained to the ibuprofen group at two hours (mean: 2.55; 95% CI: 1.22 to 3.88) after initial arch wire placement.

### Differences in pain scores on ‘occluding the front teeth’

The ANOVA differences in pain experienced on occluding the anterior teeth demonstrated that patients in the placebo group had significantly higher pain scores than patients in the ibuprofen and chewing gum groups at bedtime and at 24 hours after initial arch wire placement ($p < 0.05$) (Table II). However, the difference between the ibuprofen and chewing gum groups was not significant at any time point ($p > 0.05$). The maximum pain experienced was related to the placebo group at 24 hours (mean: 7.60; 95% CI: 6.4 to 8.7) after initial arch wire placement. Minimum pain pertained to the placebo group on day seven (mean: 3.10; 95% CI: 2.07 to 4.13) after initial arch wire placement.

### Differences in pain scores on ‘occluding the back teeth’

The ANOVA demonstrated that patients in the placebo group experienced significantly higher pain occluding the posterior teeth at bedtime and at 24 hours after initial arch wire placement ($p < 0.05$) (Table II). However, no statistically significant differences were found between the ibuprofen and chewing gum groups at any time point ($p > 0.05$). The maximum pain was again related to the placebo group at 24 hours (mean: 6.25; 95% CI: 5.01 to 7.49) after initial arch wire placement; minimum pain pertained to the chewing gum group on day seven (mean: 1.50; 95% CI: 0.15 to 2.85) after initial arch wire placement.
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Discussion

The present study compared the efficacy of chewing gum, ibuprofen and a placebo for pain relief after initial arch wire placement.

The intensity of pain experienced on performing four oral functions increased two hours after initial arch wire placement and reached maximum intensity at 24 hours. This result is in accordance with previous studies.1,11,20,23

The present results showed that the intensity of pain in the placebo group was significantly higher than that experienced in the ibuprofen and chewing gum groups at two hours, six hours, bedtime, 24 hours and two days after initial arch wire placement. However, no significant difference was found between the ibuprofen and chewing gum groups for any oral function at any time point (p > 0.05).

Profit and Fields suggested non-medication methods such as chewing gum for orthodontic pain control during orthodontic treatment.19 However, the effectiveness of chewing gum has not been widely investigated, probably because of the fear that chewing gum increases the likelihood of bracket breakage. In the present study, there was no clinically nor statistically significant difference in the frequency of appliance breakage between the ibuprofen and chewing gum groups (three and four brackets, respectively). This result confirms previous studies24,25 in which there was no evidence that chewing gum increased the level of appliance damage.

Farzanegan et al.20 reported that most people chew gum using their posterior teeth, which reduced pain in those teeth more effectively compared with the anterior teeth. Chewing gum was therefore prescribed for five minutes and at eight-hourly intervals, which

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Table II. Descriptive statistics for the three groups and repeated measures ANOVA results.

| Function | Group | 2h        | 6h        | Bedtime   | 24h        | 2d        | 3d        | 7d        |
|----------|-------|-----------|-----------|-----------|------------|-----------|-----------|-----------|
| Chewing  | Placebo | 4.25      | 6.00      | 6.30      | 6.70       | 5.05      | 4.05      | 2.60      |
|          | Ibuprofen | 1.55      | 2.45±2.62 | 2.35±2.03 | 2.58±2.58 | 3.55±2.56 | 3.70±2.43 | 4.05±1.89 |
|          | Chewing gum | 2.55±3.28 | 2.80±2.66 | 3.01±0.67 | 3.30±3.08 | 2.65±3.16 | 2.50±3.62 | 1.95±3.17 |
|          |         | [2.81-5.69] | [4.89-7.11] | [5.21-7.39] | [5.56-7.84] | [6.12-5.98] | [4.21-4.89] | [1.63-3.57] |
|          |         | P value   | 0.019*    | 0.000*    | 0.000*    | 0.000*    | 0.018*    | 0.156     | 0.577     |

| Biting   | Placebo | 4.85±3.03 | 6.35±2.30 | 6.95±2.16 | 7.65±2.32 | 6.05±2.18 | 4.95±1.76 | 3.25±2.17 |
|          | Ibuprofen | 2.55±2.83 | 3.25±2.90 | 3.10±2.78 | 4.40±3.21 | 4.70±2.86 | 3.95±2.89 | 2.85±3.01 |
|          | Chewing gum | 5.05±3.73 | 5.30±3.36 | 4.25±3.74 | 5.50±3.64 | 4.65±3.60 | 4.35±3.71 | 3.70±3.61 |
|          |         | [3.43-6.27] | [5.27-7.43] | [5.94-7.96] | [5.56-8.74] | [5.03-7.07] | [4.13-5.77] | [2.23-4.37] |
|          |         | P value   | 0.030*    | 0.004*    | 0.000*    | 0.000*    | 0.242     | 0.552     | 0.684     |

| Fitting front teeth Placebo | 3.95±2.87 | 5.95±2.72 | 6.65±2.58 | 7.60±2.43 | 6.55±2.39 | 5.40±2.66 | 3.10±2.10 |
|                            | Ibuprofen | 3.30±4.33 | 4.10±3.33 | 4.35±2.75 | 4.55±3.01 | 4.60±2.79 | 3.50±2.70 | 3.25±3.16 |
|                            | Chewing gum | 3.70±3.70 | 5.05±3.37 | 4.95±3.23 | 5.15±3.32 | 4.50±3.59 | 4.35±3.67 | 3.70±3.92 |
|                            |         | [2.60-3.30] | [4.68-7.22] | [5.44-7.86] | [6.46-8.74] | [5.43-7.67] | [4.15-6.65] | [2.07-6.13] |
|                            |         | P value   | 0.827     | 0.190     | 0.038*    | 0.004*    | 0.057     | 0.152     | 0.824     |

| Fitting back teeth Placebo | 4.55±3.30 | 5.20±2.82 | 5.55±2.87 | 6.25±2.65 | 4.30±2.31 | 3.45±2.16 | 1.90±1.74 |
|                            | Ibuprofen | 2.75±3.18 | 3.30±3.18 | 2.90±2.53 | 3.40±3.06 | 3.65±2.39 | 2.60±2.11 | 2.10±1.99 |
|                            | Chewing gum | 3.15±3.15 | 3.30±2.94 | 2.95±2.74 | 2.90±2.93 | 2.40±2.96 | 1.85±2.94 | 1.50±2.87 |
|                            |         | [3.01-6.09] | [3.88-6.52] | [4.20-6.90] | [5.01-7.49] | [3.21-5.39] | [2.44-4.46] | [1.08-2.72] |
|                            |         | P value   | 0.199     | 0.076     | 0.004*    | 0.001*    | 0.068     | 0.125     | 0.695     |

*Mean difference was significant at the 0.05 level.
varied from the present study, in which chewing gum was prescribed for 10 minutes. Pain significantly reduced in both the anterior and posterior teeth.

Hamid et al.\textsuperscript{26} compared the efficacy of ibuprofen and chewing gum for orthodontic pain relief. Chewing gum was also prescribed for five minutes at eight-hourly intervals, which produced a reduction in pain score compared with ibuprofen analgesia. In the present study, chewing gum was as effective as ibuprofen intake. The variation may be explained by the difference in appliance application as only the maxillary arch was bonded and no other pain functions were investigated.

Recently Ireland et al.,\textsuperscript{24} in a multicentre, randomised clinical trial, compared the efficacy of sugar-free chewing gum against ibuprofen for orthodontic pain relief. It was reported that patients who chewed gum used less ibuprofen compared with an ibuprofen-only group. Furthermore, there was no clinically or statistically significant difference in appliance breakage between the chewing gum and ibuprofen groups. However, the major differences between that study and the present one were no stipulation as to the types of fixed appliance, duration of gum chewing, aligning wires, ligation method, malocclusion and amount of crowding.

In addition to the local effect of gum chewing on the structure of the PDL, it seems that chewing gum has proven effects on nociceptive transmission. Mohri et al.\textsuperscript{27} explained that rhythmic gum chewing suppresses nociceptive transmission via the 5-HT (serotonergic neurons) descending inhibitory pathway, which in turn, decreases pain scores. Kamiya et al.\textsuperscript{28} reported that chewing gum for 20 minutes activated the ventral part of the prefrontal cortex and evoked augmented activity of 5-HT neurons in the dorsal raphe nucleus and therefore suppressed nociceptive responses. The study by Kamiya et al. focused on oxygenation changes in the prefrontal cortex and concluded that the analgesic effects of chewing gum were associated with a significant increase in 5-HT level in whole blood.

An additional factor that should be considered from the present study is the placebo analgesic effect. A placebo effect is mediated by the release of endogenous neuromodulators in the brain, including opioids, cholecystokinin, and dopamine.\textsuperscript{29-32} Recent studies have shown that the range of placebo response varies considerably between individuals, from no effect (‘non-responder’) to complete pain relief. Previous studies support the hypothesis that neuropsychological, genetic, and brain-related variables might predict the capacity of placebo analgesic responses in healthy subjects.\textsuperscript{33-35} Therefore, the placebo effect may have a role in reducing pain in the chewing gum groups, but its exact effect is not clear. Further research is needed to determine the individual markers of placebo responsiveness, which may help to stratify patients in clinical trials.

Because of the nature of the present study, blinding of the chewing gum group was not feasible. Accordingly, gum was chewed for only 10 minutes and further research is recommended to determine the impact of chewing gum and find the optimal chewing duration needed to reduce orthodontic pain.

Although the blinding of patients in the chewing gum group was not possible at the intervention stage, the outcome assessment was blinded, and therefore the risk of bias may be considered low. The limitation of the present study might be the uncertainty of the contribution of the placebo effect in reducing pain. The experience of pain is highly subjective and its precise evaluation is difficult.

To summarise, the present results may be limited because the current research was undertaken in a single centre by one clinician. However, chewing gum is simple, inexpensive, has no side effects and was accepted by all patients without concern.

Conclusions

In contrast to the common belief by orthodontists that chewing gum during fixed orthodontic treatment may lead to appliance breakage, it appears that chewing gum can reduce pain after orthodontic appliance activation as efficiently as ibuprofen and therefore may be a cost effective substitute for drug medication during orthodontic treatment with low risk and high acceptance.
Conflict of interest
The authors declare no conflict of interest.

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References
1. Erdinç AM, Dîncer B. Perception of pain during Orthodontic treatment with fixed appliances. Eur J Orthod 2004;26:79-85.
2. Lew KK. Attitudes and Perceptions of adults towards orthodontic treatment in an Asian community. Community Dent Oral Epidemiol 1993;21:31-5.
3. Kvam E, Gjerdet NR, Bondevik O. Traumatic ulcers and pain during orthodontic Treatment. Community Dent Oral Epidemiol 1987;15:104-7.
4. Scheurer PA, Firestone AR, Bürgin WB. Perception of pain as a result of orthodontic treatment with fixed appliances. Eur J Orthod 1996;18:349-57.
5. Furstman L, Bernick S. Clinical considerations of the periodontium. Am J Orthod Dentofacial Orthop 1972;61:138-55.
6. Skjelbred P, Lokken P. Pain and other sequelae after surgery mechanisms and management. In: Andreasen JO, Petersen JK, Laskin DM, eds. Textbook and color atlas of tooth impactions. Copenhagen, Denmark: Munksgaard, 1997;369-437.
7. Bernhardt MK, Southard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of preemptive and /or postoperative ibuprofen therapy for orthodontic pain. Am J Orthod Dentofacial Orthop 2001;120:20-7.
8. Fernandes LM, Ogaard B, Skoglund L. Pain and discomfort experienced after placement of a conventional or a superelastic NiTi aligning archwire. A randomized clinical trial. J Orofac Orthop 1998;59:331-9.
9. Jones M, Chan C. The pain and discomfort experienced during orthodontic treatment: a randomized controlled clinical trial of two initial aligning archwires. Am J Orthod Dentofacial Orthop 1992;102:373-81.
10. Polat O, Karaman AI. Pain control during fixed orthodontic appliance therapy. Angle Orthod 2005;75:214-9.
11. Ngan P, Wilson S, Shanfeld J, Amini H. The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. Am J Orthod Dentofacial Orthop 1994;106:88-95.
12. Bloom BS. Over the counter NSAIDs and GI side effects [abstract 23]. Int Soc Technol Assess Health Care 2001;17.
13. Ecklund CR, Ross MC. Over-the-counter medication use in preschool children. J Pediatr Health Care 2001;15:168-72.
14. American Academy of Family Physicians. Health information for the whole family, OTC drugs: reducing the risk of adverse effects. Viewed 18 July 2008, <http://familydoctor.org/online/famdocen/home/otcenter/basics/853.html>.
15. Lim HM, Lew KK, Tay DK. A clinical investigation of the efficacy of low level laser therapy in reducing orthodontic postadjustment pain. Am J Orthod Dentofacial Orthop 1995;108:614-22.
16. Bayani S, Rostami S, Ahrari F, Sacedipouraya I. A randomized clinical trial comparing the efficacy of bite wafer and low level laser therapy in reducing pain following initial arch wire placement. Laser Ther 2016;25:121-9.
17. Roth PM, Thrash WJ. Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. Am J Orthod Dentofacial Orthop 1986;90:132-8.
18. Weiss DD, Carver DM. Transcutaneous Electrical Neural Stimulation for Pain Control. J Clin Orthod 1994;28:670-1.
19. Profit WR, Fields HW. Biologic basis of orthodontic therapy. In: Profit WR, Fields HW, eds. Contemporary Orthodontics. 3rd edn. St Louis: Mosby, 2000.
20. Farzanegan F, Zebjarad SM, Alizadeh S, Ahrami F. Pain reduction after initial archwire placement in orthodontic patient: a randomized clinical trial. Am J Orthod Dentofacial Orthop 2012;141:169-73.
21. White IW. Pain and cooperation in orthodontic treatment. J Clin Orthod 1984;18:572-5.
22. Hwang JY, Tee CH, Huang AT, Taft L. Effectiveness of thera-bite wafers in reducing pain. J Clin Orthod 1994;28:291-2.
23. Steen Law SL, Southard KA, Law AS, Logan HL, Jakobsen JR. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am J Orthod Dentofacial Orthop 2000;118:629-35.
24. Ireland AJ, Ellis P, Jordan A, Bradley R, Ewings P, Attack NE et al. Comparative assessment of chewing gum and ibuprofen in the management of orthodontic pain with fixed appliances: A pragmatic multicenter randomized controlled trial. Am J Orthod Dentofacial Orthop 2016;150:220-7.
25. Benson PE, Razi RM, Al-Bloushi RJ. The effect of chewing gum on the impact, pain and breakages associated with fixed orthodontic appliances: a randomized clinical trial. Orthod Craniofac Res 2012;15:178-87.
26. Hamid WU, Haq AU, Mahmood HS, Azem M, Irfan S. Comparison between ibuprofen and chewing gum for orthodontic pain control. Pak Oral Dent J 2016;36:79-83.
27. Mohri Y, Fumoto M, Sato-Suzuki I, Umino M, Arita H. Prolonged rhythmic gum chewing suppresses nociceptive response via serotoninergic descending inhibitory pathway in humans. Pain 2005;118:35-42.
28. Kamiya K, Fumoto M, Kikuchi H, Sekiyama T, Mohri-Lizuawa Y, Umino M et al. prolonged gum chewing evokes activation of the ventral part of prefrontal cortex and suppression of nociceptive responses: involvement of the serotonin system. J Med Dent Sci 2010;57:35-43.
29. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 2009;63:533-43.
30. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppa RA, Zubierta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 2008;65:220-31.
31. Wager TD, Scott DJ, Zubierta JK. Placebo effects on human mu- opioid activity during pain. Proc Natl Acad Sci USA 2007;104:11056-61.
32. Zubierta JK, Buellera JA, Jackson LR, Scott DJ, Xu Y, Koeppa RA et al. Placebo effects mediated by endogenous opioid activity on mu- opioid receptors. J Neurosci 2005;25:7754-62.
33. Hall KT, Lembo AJ, Kirsh I, Ziegas DC, Douaihier J, Jensen KB et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One 2012;7:e48135.
34. Pecita M, Azhar H, Love TM, Lu T, Fredrickson BL, Stohler CS et al. Personality trait predictors of placebo analgesia and neurobiological correlates. Neuropsychopharmacology 2013;38:639-46.
35. Stein N, Sprenger C, Scholz J, Wietch K, Bingel U. White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. Pain 2012;153:2210-7.