ORIGINAL RESEARCH

Effect of an Anesthetic Chewing Gum on the Initial Pain or Discomfort from Orthodontic Elastomeric Separator Placement

Manal A Al-Melh[1], Aly Nada[2], Hanan Badr[3], Lars Andersson[4]

Abstract

Aim: The aim of this study was to investigate the effect of a formulated anesthetic chewing gum (ACG) on the initial pain/discomfort resulting from the placement of orthodontic separators.

Materials and methods: The preparation of ACG formulation was investigated using food and drug administration (FDA)-certified ingredients. Sixty subjects were recruited and randomly allocated to three groups: (1) ACG, (2) chewing gum (CG) without anesthetics or (3) control (no CG) group. All subjects received an orthodontic elastomeric separator that was placed between the maxillary right or left first molar and second premolar. For all groups, the registration of pain/discomfort experienced immediately after separator placement (0 hour), then after 1, 4, and 8 hours was carried out using the visual analog scale.

Results: Regarding the pain/discomfort perception, there was a statistically significant difference (p value <0.0001) between the three groups (ACG, CG, and controls) at each of the three-time points (1, 4 and 8 hours). There were no harms reported by both groups except for temporary mild muscle soreness from gum chewing that was reported by four subjects from the ACG group and two subjects from the CG group.

Conclusion: The ACG can significantly decrease and eliminate the initial pain/discomfort resulting from the placement of the orthodontic elastomeric separators. Furthermore, the ACG may decrease the need for a systemic analgesic.

Clinical significance: Orthodontic elastomeric separator placement can be uncomfortable. The ACG significantly decreased the initial pain/discomfort from orthodontic separators during the 8 hours. Therefore, the ACG can be used by the patients as needed whenever pain/discomfort is experienced from the placement of elastomeric separators. Consequently, this may reduce the need for systemic analgesics.

Keywords: Anesthesia, Chewing gum, Discomfort, Pain, Separators.

The Journal of Contemporary Dental Practice (2019): 10.5005/jp-journals-10024-2708

Introduction

The placement of orthodontic elastomeric separators can be considered as one of the uncomfortable and painful orthodontic procedures.[1,2] Tooth separation can have an undesirable impact on patients chewing, daily activity, and sleep.[3] This disturbing experience can eventually affect the patients' acceptance and compliance with the orthodontic treatment.[4]

The literature has revealed various techniques trying to manage the pain related to orthodontic procedures, including orthodontic elastomeric separator placement.[5,6] One of the suggested methods for controlling orthodontic pain was the use of CG. It has been shown that chewing on gum or plastic wafer during the first few hours of appliance activation can reduce the consequential pain.[7]

In addition to the use of CG to control orthodontic pain, topical anesthetics confirmed to be very effective in reducing or eliminating pain associated with needle stick injections, suturing of facial lacerations, and different orthodontic procedures.[8–16] More recently, a study shows that the lidocaine/prilocaine (L/P) gel can significantly reduce pain from immediate placement of orthodontic elastomeric separators.[17]

Medicated CG is an effective drug delivery system intended for either local or systemic treatment.[18] It was reported that 63% of the patients reported less discomfort after chewing aspirin-containing CG following orthodontic procedures.[19,20]

However, to date, there is no current information in the literature on the effect of an L/P anesthetic-containing CG on orthodontic pain. Therefore, the aims of this study were to design an optimized ACG tablet formulation containing a combination of two local anesthetic agents and to investigate the effect of the ACG on pain/discomfort resulting from the initial placement of the orthodontic elastomeric separators.

[1]Department of Developmental and Preventive Sciences, Faculty of Dentistry, Health Sciences Center, Kuwait University, Kuwait City, Kuwait

[2]Department of Pharmaceutics, Faculty of Pharmacy, Health Sciences Center, Kuwait University, Kuwait City, Kuwait

[3]Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait City, Kuwait

[4]Department of Surgical Sciences, Faculty of Dentistry, Health Sciences Center, Kuwait University, Kuwait City, Kuwait

Corresponding Author: Manal A Al-Melh, Department of Developmental and Preventive Sciences, Faculty of Dentistry, Health Sciences Center, Kuwait University, Kuwait City, Kuwait, Phone: +965 24636709, e-mail: mabualmelh@hsc.edu.kw

How to cite this article: Al-Melh MA, Nada A, Badr H, *et al.* Effect of an Anesthetic Chewing Gum on the Initial Pain or Discomfort from Orthodontic Elastomeric Separator Placement. J Contemp Dent Pract 2019;20(11):1286–1292.

Source of support: Nil

Conflict of interest: None

Materials and Methods

Study Design and Ethical Approval

This is a case-control study that was conducted at Kuwait University, Faculty of Dentistry Dental Clinic in Kuwait. The study's drug

formulation, design, and protocol were approved by the Ethical Committee of the Health Sciences Center at Kuwait University. The subjects' rights were protected, and written informed consent was obtained from all the subjects participating in this study.

ACG Formulation

The preparation of local anesthetic-containing CG formulation was investigated using Food and Drug FDA-certified ingredients. The ACG tablets were created from raw materials in collaboration with the Faculty of Pharmacy, Department of Pharmaceutics at Kuwait University, Kuwait.

Several preliminary trials were performed to optimize the anesthetic drug content, taste, the local anesthetic duration, and other necessary functional excipients to prepare the CG tablets. Each tablet contained 2 mg of each of the two tested local anesthetics, which were lidocaine and prilocaine. Table 1 shows the final optimized formulation adopted for the manufacturing of the anesthetic gum tablets.

The method of manufacturing and the type of inactive additives served to mask the bitter taste of the drugs and improved the taste acceptability. Sweeteners and flavoring agents were used to overcome the bitterness of the CG tablets (Table 1). This was tested by a panel of experts to enhance the subjects' compliance and adherence to the instructions of use. In addition, the choice of additives ensured smooth and consistent manufacturing of the dosage forms, such as the ease of flow of the granulations as well as direct compression into tablets.

As tested by a panel of experts, it was observed that the anesthetic effect of the CG started 3–5 minutes from chewing the gum. Also, the anesthetic effect of the CG lasted for about 15 minutes after chewing one gum tablet, and the anesthetic effect lasted for almost 25 minutes after chewing two gum tablets.

Table 1: Materials used in formulation development of the anesthetic chewing gum tablets

Ingredient	*Role of ingredient*	*Supplier*	*Quantity (mg/tablet)*
Lidocaine HCl	Anesthetic drug	Zhengzhou Sigma Chemical Co., Ltd., China	2
Prilocaine HCl	Anesthetic drug	Zhengzhou Sigma Chemical Co., Ltd., China	2
Health in gum	Chewing gum base	Cafosa Gum, Spain	436
Sorbitol	Sweetener	Spectrum, USA	15
Mannitol	Secondary sweetener	Loba Chemie, India	15
Talc	Anti-adherent	Sigma Aldrich, USA	10
Magnesium stearate	Lubricant	Aldrich, Germany	5
Titanium dioxide	Opacifier	Aldrich, USA	5
Colloidal silicon dioxide (Aerosil®)	Glidant	Evonik, Germany	2.5
Peppermint oil	Flavoring agent	Fluka, Switzerland	2.5
Menthol	Flavor enhancer	Sigma Aldrich, USA	5

Therefore, it was agreed the use of two ACG tablets provided acceptable taste and sufficient anesthetic duration.

The ACG tablets were off-white and round with a smooth curved surface (Fig. 1). The tablets had a mint odor, and they were free from any physical flaws. As tested by a panel of experts, the taste and consistency of the ACG tablets were acceptable. The dimensions of the tablets were measured and found to be uniform with an average diameter of 10.02 mm ± 0.040 mm, average thickness of 6.56 mm ± 0.119 mm, and average weight of 499.65 mg ± 0.381 mg. In addition, the dimensions of the tablets complied with the United States Pharmacopeia (USP) weight variation requirements (NMT ± 5%).[21]

Participants, Eligibility Criteria, and Settings

In this study, 67 adult healthy voluntary subjects, between 23 years and 41 years of age, were approached. The subjects were undergraduate 7th-year dental students (n = 13), academic staff members including assistant professors (n = 8), and dental assistants (n = 46) from the Faculty of Dentistry, Kuwait University, Kuwait.

Each participant was eligible to participate if the following inclusion criteria were fulfilled: (1) medically healthy with no history of allergies to any of the anesthetic components, (2) healthy temporomandibular joints, (3) healthy gingival tissues, (4) sound and intact posterior teeth and (5) tight interproximal contact point between the right or left maxillary 1st molar and 2nd premolar where the orthodontic elastomeric separator was going to be applied. The tightness of the contact between the 1st molar and 2nd premolar was checked with a piece of waxed dental floss. Pregnant women, subjects with systemic diseases, and subjects taking systemic analgesics were excluded from this study.

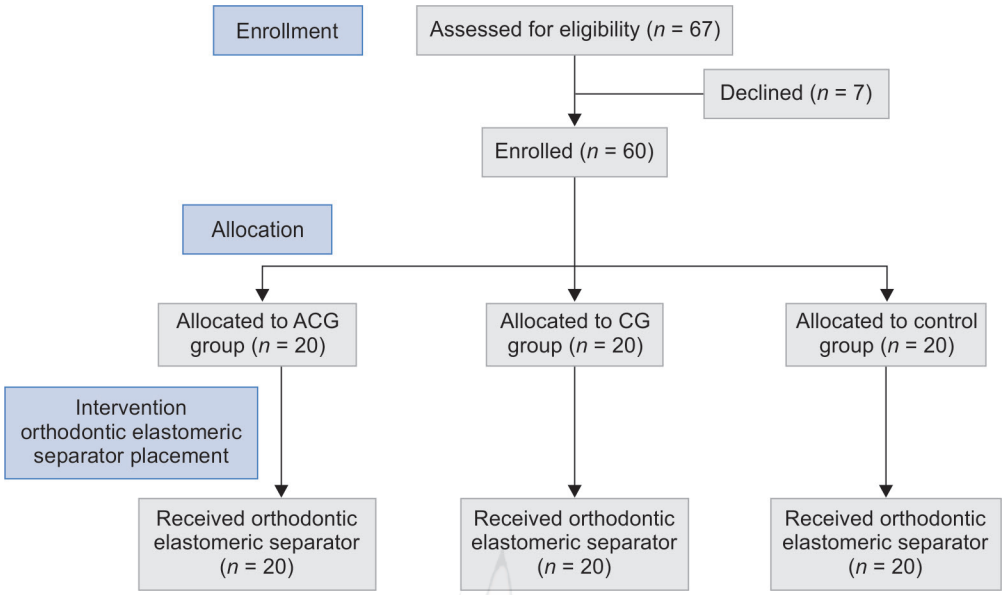
Sample

Flowchart 1 shows the sample allocation diagram, which describes the patient flow throughout the study. Out of 67 subjects, 7 declined or were not fit for participation. The 60 subjects were eligible to participate in the study, with 89.6% response rate.

Three groups of subjects (20 in each) were randomly created, and the eligible subjects received a full explanation about the process. Once participants had the orthodontic elastomeric separator placed, they were randomly allocated to one of the three groups: the ACG group, the CG without anesthetic (CG) group and

Fig. 1: Anesthetic chewing gum tablets

Flowchart 1: Sample enrollment diagram



the control group, which did not receive any type of CG or any type of pain/discomfort relief remedy. All three groups received elastomeric separators for a total duration of 8 hours.

Blinding

The clinician and the subjects were not blinded to the intervention, which was the orthodontic elastomeric separator placement. However, the subjects in both the ACG and CG groups were unaware of the type and constituents of the CG given, whether it was CG with an anesthetic (ACG) or CG without anesthetic (CG). Furthermore, the subjects were asked not to discuss their experience from the CG given with the other participants.

Interventions

The subjects were encouraged to have a good breakfast before the start of the procedure as they, for pain/discomfort registration, were advised to try to refrain from eating during the study except during lunchtime. The subjects could drink fluids throughout the study. The subjects who received with the ACG or CG were further informed to stop chewing the gum during the 1-hour lunch break and to resume chewing the ACG right after lunch.

The method for the orthodontic elastomeric separator placement involved the use of dental floss. The separator was placed between the maxillary 2nd premolar and 1st molar on the right or left side of all subjects. The sides where the separator was placed were alternated so that in each group, ten subjects received the separator on the right side, and ten subjects had the separator placed on the left side.

After immediate placement of the elastomeric separator, the subjects in all groups were instructed to register their pain/discomfort response after the immediate placement of the separator (0 hour), after 1, 4, and 8 hours from the separator placement. All the subjects from the three groups had the orthodontic elastomeric separator placed at 9 am and removed at 5 pm. After the eighth hour, the separator was removed from each subject with an explorer.

Fig. 2: Chewing gum tablet

Anesthetic Chewing Gum Group ($n = 20$)

After the allocation of the subjects to the ACG group, a blank white container consisting of a total of 36 sterile ACG tablets was given to each subject.

Each subject was asked to start chewing on the first two CG tablets once the separator was placed and after the recording of the immediate response (0 hour). The subjects were instructed to chew only on the side where the separator was placed.

The subjects were instructed to chew on two new gum tablets every 25 minutes during the 8-hour duration except for the lunch hour break.

Chewing Gum without Anesthetic Group (CG) ($n = 20$)

After the allocation of the subjects to the CG group, a sealed blank white container containing the CG tablets was given to each subject. The type of CG given to this group was Mentos White® (Perfetti Van Melle, Vietnam), which is a xylitol sugar-free CG with a sweet mint flavor (Fig. 2).

From the manufacturer, the sealed Mentos White® CG container comprised of 38 CG tablets, and each CG tablet had a thickness of 8.4 mm, a diameter of 15.9 mm and a weight of 1.5 g.

The sticker containing the logo of the CG brand was removed from the container to obscure the subject from the type of CG given. The subjects were instructed to consume only the amount needed of the CG until completion of the study, which was 17 CG tablets.

As with the ACG group, similar instructions were given to the CG group regarding the use of CG and the recording of pain/discomfort experience.

Control Group ($n = 20$)

The subjects in the control group were not given any type of pain remedy. The subjects were instructed not to chew any type of CG or take any kind of systemic analgesic. It was explained to the subjects that they should avoid eating during the 8-hour duration except during the 1-hour lunchtime. If they needed to eat, they were advised to chew on the side, which did not contain the elastomeric separator.

Registration of Pain

Registration of pain/discomfort sensation was recorded on a visual analog scale (VAS) after immediate placement of the elastomeric separators (0 hour), after 1, 4, and 8 hours. The overall pain perception was measured by the subjects using a scale from 0 mm to 100 mm horizontal nongraded VAS, with the left endpoint "0" marked as "no pain/discomfort," and the right endpoint "100" marked "worst possible pain/discomfort."

Interview

After completion of the study, the subjects who received either the ACG or CG were interviewed regarding the effectiveness and taste of the CG provided. In addition, the subjects from the ACG and CG groups were questioned whether there were any local or systemic side effects experienced from the CG used. Moreover, the subjects from all three groups were asked if they observed any adverse effects from the orthodontic elastomeric separator placement.

Statistical Analysis

Data were entered and analyzed using SPSS version 24 (IBM, U.S.A.). Mean (SD) and median were used for descriptive statistics. The value of pain perception among the ACG, CG, and control groups at different time intervals was tested for normality using the Shapiro–Wilk test, which showed a p value of <0.001, indicating a not normal distribution. A nonparametric test, Kruskal–Wallis test was performed to test the differences in the median of pain perception scores among the ACG, CG, and control groups. A p value of <0.05 was considered as the significance level.

Results

Pain Perception

The pattern of pain perception among the ACG group, the CG group, and the control group at different points of time is illustrated in Figure 3. The figure demonstrated the mean pain perception at placement (0 hour), which was "20 mm" for the ACG group, "15 mm" for the CG group, and "27 mm" for the control group.

As for the ACG group, the mean pain perception score showed decreasing values during the first hour of separator placement from "20 mm" to almost "0 mm". In addition, the pain perception remained at the "0 mm" level in the next two measures, which were at 4–8 hours after using the ACG.

In comparison with the ACG group, figure 3 also demonstrated that the mean pain perception score showed a lesser decrease among the control group after 1-hour, which was from "27 mm" to "11 mm". In contrast to the ACG group, the pain perception among the control group started to increase gradually to reach a means of "16 mm" and "21 mm" at 4 hours and 8 hours, respectively.

As for the CG group, it was shown in the figure that the mean pain perception score showed the least decrease, which was from "15 mm" to "13 mm" after 1-hour, as compared to the ACG and control groups. Also, in contrast to the ACG group, the pain perception among the CG group remained the same from the first hour to the fourth hour, but it started to progressively increase to a mean of "19 mm" at the eighth hour.

The mean and median (minimum, maximum) of pain perception among the ACG, CG, and control groups at the time of placement of separators (0 hour), at 1 ,4, and 8 hours was illustrated in Table 2. At the zero point, the median of pain perception showed no significant differences between the three groups.

However, the median of pain perception was equal to "0 mm" at 1, 4, and 8 hours after separator placement among the ACG group, which was less than that reported by the control group, which was 5.5 mm, 13.0 mm, and 6.0 mm, respectively. In addition, the median of pain perception among the ACG group was also significantly less than that reported by the CG group, which was 9.0 mm, 10.0 mm, and 18.0 mm, respectively. Nevertheless, at the eighth hour, the median of pain perception was higher in the CG group (18.0 mm) as compared to the control group (6.0 mm). The differences in the median of pain perception between the ACG, CG, and control groups at each of the three-time points (1, 4, and 8 hours) were highly significant, demonstrating a p value of <0.0001.

These results of the present study illustrated that using the ACG tablets that contained a combination of the two local anesthetic agents showed a considerable relief of pain/discomfort resulting from the initial placement of the orthodontic elastomeric separators.

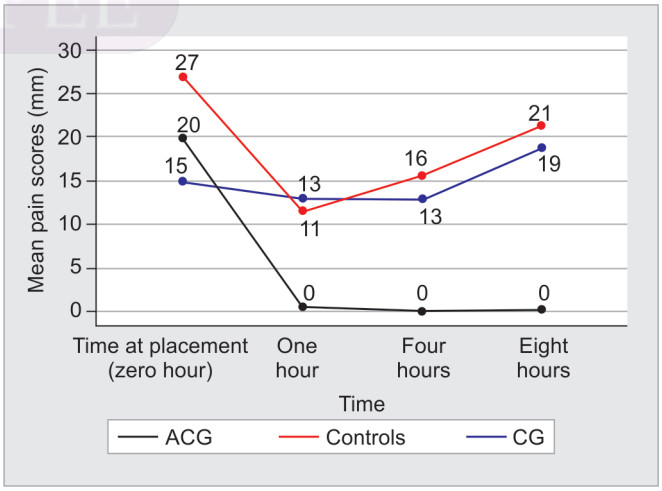


Fig. 3: Mean of pain perception at different times after providing chewing gum to the anesthetic chewing gum group ($n = 20$), chewing gum group ($n = 20$) and control group ($n = 20$)

Table 2: Mean and median (min, max) pain perception at different points of time among the anesthetic chewing gum (ACG) group ($n = 20$), chewing gum (CG) group and control group ($n = 20$)

	ACG group n = 20		*CG group n = 20*		*Control group n = 20*		
Time	*Median (min, max)*	*Mean*	*Median (min, max)*	*Mean*	*Median (min, max)*	*Mean*	*p value**
Time at placement (0 hour)	16.0 (2.0, 80.0)	19.9	11.5 (1.0, 35.0)	15.0	23.0 (3.0, 90.0)	27.0	0.209
1 hour	0.0 (0.0, 4.0)	0.4	9.0 (2.0, 42.0)	11.5	5.5 (0.0, 46.0)	13.0	<0.0001
4 hours	0.0 (0.0, 4.0)	0.0	10.0 (0.0, 54.0)	13.0	13.0 (0.0, 42.0)	15.6	<0.0001
8 hours	0.0 (0.0, 3.0)	0.2	18.0 (0.0, 60.0)	18.8	6.0 (0.0, 91.0)	21.2	<0.0001

*Kruskal–Wallis test

Discussion

The instant placement of orthodontic elastomeric separators can be uncomfortable or painful for some patients.[17] Chewing gum has been proven to be an effective way to reduce pain resulting from certain orthodontic procedures.[22] The present study showed that the ACG was more effective in reducing or eliminating pain/discomfort from initial orthodontic elastomeric separator placement than a CG that does not contain an anesthetic effect.

In the present study, it was shown that for the three groups, the pain/discomfort was present immediately at the placement of the elastomeric separator (0 hour). Then, the pain started to increase from the first hour and reached its maximum at 8 hours among the CG and control groups. However, this pattern was not the same among the ACG group, where the effect of CG eliminated the pain/discomfort perception at 1-hour and continued to the eighth hour.

The results of the present study match with a study done by Otasevic et al., which demonstrated that after the placement of fixed appliances, patients who used the bite wafers reported more pain than those who avoided masticatory activity.[23] In the present study, it was shown that for the CG group, the median of pain perception was increasing at the first, fourth, and eighth hours. This suggests that the CG given to the CG group was not enough to reduce the pain/discomfort from the initial placement of orthodontic separators. Also, to most of the subjects in the CG group, the process of chewing the gum was uncomfortable, and it exacerbated the pain/discomfort from the orthodontic separator. This may explain the difference in median of pain perception between the CG group and the control group in the eighth hour.

Moreover, Ireland et al. showed that the CG group experienced slightly more pain on the day of bonding, but the pain decreased in the following 3 days.[24] In the present study, the CG and control groups experienced pain/discomfort after the immediate placement of the separators and up to 8 hours.

The duration of the present study was 8 hours, which marks the initial period of pain/discomfort from the elastomeric separator placement. Pain usually begins 2 hours after the orthodontic force application reaches its peak at 24 hours and lasts for 5–7 days.[25] Asiry et al. conducted a study on adolescent Saudi orthodontic patients, and they showed that the tenderness and pain associated with orthodontic separation starts and peaks within 4–48 hours from separator placement.[26] It would be interesting in the future to study the effect of the ACG for 2 days when the pain is usually at its peak.

The anesthetic constituents used in the ACG were 2 mg of lidocaine and 2 mg of prilocaine (L/P). The reason for choosing such materials was that the L/P topical anesthetic effect was proven to be potent for various dental and orthodontic procedures.[8,10–12,17] When subjects in the ACG group were interviewed, all of them mentioned that the numbness experienced from the CG was sufficient, and some further described it as being satisfactorily intense.

The L/P constituents of the CG used in the present study were selected based on a literature report by Friskopp et al., which demonstrated that the 2.5% lidocaine and 2.5% prilocaine topical anesthetic Oraqix® had a quick onset of action of 30 seconds and duration of action of almost 17–20 minutes when used for periodontal pocket assessment.[27] According to Al-Melh and Andersson, it was shown that Oraqix® was effective from the second minute after application on the vestibular and palatal mucosae.[11,12] In the present study, the ACG analgesic effect was evident at initial consumption and remained effective throughout the study.

In the present study, a total of 36 CG tablets were given to subjects in the ACG group who were instructed to chew on two tablets every 25 minutes to ensure the effectiveness of the anesthetic component of the CG. The reason for such instructions was based on an initial trial of the ACG by a panel of experts that occurred during the creation of the ACG tablets. A consensus showed that chewing two gum tablets was more effective than one gum tablet. Moreover, it was reported that the anesthetic effect of the ACG started 3–5 minutes after chewing one or two gum tablets. The anesthetic effect of the ACG started to diminish after about 10–15 minutes when chewing one gum tablet and around 20–25 minutes after chewing two gum tablets.

The reasons behind choosing Mentos White® CG for the CG group were because of its refreshing and long-lasting flavor, its sugar-free quality, and the inclusion of xylitol to protect the teeth. Also, the CG tablets are manufactured in a convenient bottle with a securely sealed lid, which made it easy to handle. To prevent cross contamination, it was preferred that the subjects will unseal the container at the start of the study.

It would have been advantageous to create the CG tablets with the same dimensions and hardness as the ACG tablets. However, due to the limited laboratory resources to provide enough CG tablets, the inadequate availability of the raw materials, and the shortage of manpower, it was difficult to provide such tablets.

The subjects from the ACG and CG groups were interviewed to inquire about the effectiveness and taste of the CG. All subjects in the ACG group reported that the numbness from the CG was enough and evident a few minutes after consumption. Most of the subjects reported that the anesthetic effect was still present after 25 minutes and before chewing on the next two ACG tablets. Regarding the flavor of the ACG, nine out of 20 reported that the taste of the ACG needed improvement by adding more mint flavor. All subjects from the CG group liked the taste of the Mentos White® CG, which was a sweet mint flavor.

The subjects from all three groups were asked if there were any adverse effects associated with the elastomeric separator placement. Four subjects in the ACG and two subjects in the CG group reported mild muscle soreness from gum chewing, which disappeared after completion of the study. Also, three subjects in the ACG group and five subjects in the CG group stated that the CG tends to stick to the elastomeric separator at times during chewing. However, this problem can be solved by improving the consistency of CG.

Also, 17 subjects from the CG group mentioned that the act of chewing the gum was uncomfortable and made the pain/discomfort worse. The subjects in all three groups reported no adverse effects related to the orthodontic elastomeric separator placement.

It has been reported by Friskopp and Huledal and Herdevall et al., that there is a large safety margin regarding the systemic effects following the application of L/P topical anesthetic Oraqix®. The plasma profiles of lidocaine and prilocaine following a single dose of Oraqix® to adult patients with advanced periodontitis were low in comparison to those reported to cause initial signs of CNS toxicity.[28,29] Adverse effects of methemoglobinemia after the use of topical L/P cream have been reported in infants and newborns.[30] In the present study, the sample comprised of only adults, and the L/P constituents of the CG used caused no reported local or systemic adverse reactions.

It is important to acknowledge the limitations of the present study. One of the limitations was the small sample size. Another limitation was inadequate laboratory resources to provide CG tablets without anesthetic agents.

Conclusion

The ACG can be easily used by the orthodontic patients when pain or discomfort is initially experienced after the placement of orthodontic elastomeric separators. Moreover, the ACG can reduce the need for systemic analgesics, such as ibuprofen, which is known to cause adverse effects in some patients.

Clinical Significance

Orthodontic elastomeric separator placement can be uncomfortable. The ACG significantly decreased the initial pain/discomfort from orthodontic separators during the 8 hours. Therefore, the ACG can be used by the patients whenever pain/discomfort is firstly experienced from the placement of elastomeric separators. Consequently, this may reduce the need for systemic analgesics.

Acknowledgments

Authors would like to thank all the volunteers who participated in this study.

References

1. Krishnan V. Orthodontic pain: from causes to management—a review. Eur J Orthod 2007;29(2):170–179. DOI: 10.1093/ejo/cjl081.
2. Polat O. Pain and discomfort after orthodontic appointment. Semin Orthod 2007;13:292–300. DOI: 10.1053/j.sodo.2007.08.010.
3. Nalbantgil D, Cakan DG, Oztoprak MO, et al. Perception of pain and discomfort during tooth separation. Aust Orthod J 2009;25(2): 110–115.
4. Bernabë E, Sheiham A, de Oliveira CM. Impacts on daily performances related to wearing orthodontic appliances. Angle Orthod 2008;78(3):482–486. DOI: 10.2319/050207-212.1.
5. Long Hu, Wang Yan, Jian Fan, et al. Current advances in orthodontic pain. Int J Oral Sci 2016;8(2):67–75. DOI: 10.1038/ijos.2016.24.
6. Shenoy N, Shetty S, Ahmed J, et al. The pain management in orthodontics. J Clin Diagn Res 2013;7(6):1258–1260. DOI: 10.7860/JCDR/2013/4860.3036.
7. Proffit WR. Contemporary orthodontics, 4th ed. St. Louis: Mosby; 2000.
8. Keim RG. Managing orthodontic pain. J Clin Orthod 2004;38:641–642.
9. Friedman PM, Mafong EA, Friedman ES, et al. Topical anesthetics update: EMLA and beyond. Dermatol Surg 2001;27(12):1019–1026. DOI: 10.1097/00042728-200112000-00006.
10. Abu Al-Melh M, Andersson L, Behbehani E. Reduction of pain from needle stick in the oral mucosa by topical anaesthetics: a comparative study between lidocaine/prilocaine and benzocaine. J Clin Dent 2005;16(2):53–56.
11. Al-Melh MA, Andersson L. Comparison of topical anesthetics (EMLA/Oraqix vs benzocaine) on pain experienced during palatal needle injection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(5):e16–e20. DOI: 10.1016/j.tripleo.2006.11.033.
12. Al-Melh MA, Andersson L. Reducing pain from palatal needle stick by topical anesthetics: a comparative study between two lidocaine/prilocaine substances. J Clin Dent 2008;19(2):43–47.
13. McNulty RJ, Handley TP, Devlin MF. Reducing the need for general anaesthesia in children: use of LAT gel in treating facial lacerations. Br J Oral Maxillofac Surg 2013;51(6):e130–e131. DOI: 10.1016/j.bjoms.2012.04.259.
14. Musawi AA, Andersson L. Use of topical as only anesthetic for suturing a traumatic facial laceration. Dent Traumatol 2010;26(3):292–293. DOI: 10.1111/j.1600-9657.2010.00881.x.
15. Meechan JG. The use of EMLA for an intraoral soft-tissue biopsy in a needle phobic: a case report. Anesth Prog 2001;48(1):32–34.
16. Al-Asfour A, Al-Melh M, Andersson L, et al. Healing pattern of experimental soft tissue lacerations after application of novel topical anesthetic agents—an experimental study in rabbits. Dent Traumatol 2008;24(1):27–31. DOI: 10.1111/j.1600-9657.2006.00482.x.
17. Al-Melh M, Andersson L. The effect of a lidocaine/prilocaine topical anesthetic on pain and discomfort associated with orthodontics elastomeric separator placement. Prog Orthod 2017;18((1):1. DOI: 10.1186/s40510-016-0156-7.
18. Gadhavi AG, Patel BN, Patel DM, et al. Medicated chewing gum-A 21st century drug delivery system. Int J Pharm Sci Res 2011;2:1961–1974.
19. Washington N, Washington C, Wilson C. Physiological pharmaceutics: barriers to drug absorption. NY: CRC Press, Taylor and Francis; 2001.
20. White LW. Pain and cooperation in orthodontic treatment. J Clin Orthod 1984;18(8):572–575.
21. United States Pharmacopeia (USP 38). The U.S. Pharmacopeial Convention. Rockville: MD 20852-1790, Vol. 1; 2015.
22. Benson PE, Razi RM, Al-Bloushi RJ. The effect of chewing gum on the impact, pain and breakages associated with fixed orthodontics appliances: a randomized clinical trial. Orthod Craniofac Res 2012;15(3):178–187. DOI: 10.1111/j.1601-6343.2012.01546.x.
23. Otasevic M, Naini FB, Gill DS, et al. Prospective randomized clinical trial comparing the effects of a masticatory bite wafer and avoidance of hard food on pain associated with initial orthodontic tooth movement. Am J Orthod Dentofac Orthop 2006;130(1):e9–e15. DOI: 10.1016/j.ajodo.2005.11.033.
24. Ireland AJ, Ellis P, Jordan A, 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 Dentofac Orthop 2016;150(2):220–227. DOI: 10.1016/j.ajodo.2016.02.018.
25. Polat O, Karaman AI. Pain control during fixed orthodontic appliance therapy. Angle Orthod 2005;75(2):214–219. DOI: 10.1043/0003-3219(2005)075<0210:PCDFOA>2.0.CO;2.
26. Asiry MA, Albarakati SF, Al-Marwan MS, et al. Perception of pain and discomfort from elastomeric separators in Saudi adolescents. Saudi Med J 2014;35(5):504–507.
27. Friskopp J, Nilsson M, Isacsson G. The anesthetic onset and duration of a new lidocaine/prilocaine gel intra-pocket anesthetic (Oraqix)

for periodontal scaling/root planing. J Clin Periodontol 2001;28(5): 453–458. DOI: 10.1034/j.1600-051x.2001.028005453.x.
28. Friskopp J, Huledal G. Plasma levels of lidocaine and prilocaine after application of Oraqix, a new intrapocket anesthetic, in patients with advanced periodontitis. J Clin Periodontol 2001;28(5):425–429. DOI: 10.1034/j.1600-051x.2001.028005425.x.
29. Herdevall BM, Klinge B, Persson L, et al. Plasma levels of lidocaine, o-toluidine, and prilocaine after application of 8.5 g Oraqix in patients with generalized periodontitis: effect on blood methemoglobin and tolerability. Acta Odontol Scand 2003;61(4):230–234. DOI: 10.1080/00016350310004106.
30. Kuiper-Prins E, Kerkhof GF, Reijnen CG, et al. A 12-day-old boy with methemoglobinemia after circumcision with local anesthesia (lidocaine/prilocaine). Drug Saf Case Rep 2016;3(1):12. DOI: 10.1007/s40800-016-0033-9.