Does Benzocaine Toothpaste Have More Pain-Relieving Effect Compared To Placebo Toothpaste In Orthodontic Patients? A Double-Blind Randomized Controlled Trial

Ladan Eslamian
Shahid Beheshti University of Medical Sciences
Sepideh Soheilifar (se.soheilifar@gmail.com)
Orthodontist
Sanaz Soheilifar
Orthodontist
Seyed Alireza Mortazavi
Shahid Beheshti University of Medical Sciences

Research Article

Keywords: benzocaine, orthodontic appliances, pain, randomized controlled trial

Posted Date: September 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-866567/v1

Abstract

Background:

Pain management in fixed orthodontic treatment is an important challenge. None of the present methods has been successful in pain relief. The objective of this double-blind cross-over trial was to compare the effect of benzocaine-contained toothpaste and placebo toothpaste on relieving pain caused by fixed orthodontic treatment.

Methods and material:

Patients undergoing fixed orthodontic treatment at Shahid Beheshti University of Medical Sciences with experience of pain in previous appointment were randomly assigned into 3 groups of 5% benzocaine-contained toothpaste, placebo toothpaste and control group. Eligibility criteria included being in leveling and alignment stage, 6-8 mm space deficiency, no acute or chronic pain or frequent consumption of analgesic drugs. Patients were instructed to use toothpastes 3 times in a day. Main outcome was pain experienced by patients according to Visual Analogue Scale at 8 different time intervals in 7 days. Randomization was done with random numbers in opaque envelopes for sequence of appointments. Blinding was applicable for patients, operator and outcome assessor. Data analysis was done with repeated measure ANOVA for assessing overall effect and Bonferroni for pairwise analysis. P value was assigned to be 0.05.

Results:

From 33 patients who participated in the study, 27 patients (23 females and 4 males) completed the study. Each patient was randomly allocated to all 3 groups in cross-over design. Mean pain in benzocaine group was less than the placebo and control group (28.63± 25.43, 31.31± 22.09 and 31.20 ± 24.09, respectively). Benzocaine toothpaste group experienced statistically significantly less pain than the other two groups at 2 hours (P 0.015). No adverse event was observed in patients.

Conclusion:

Benzocaine contained toothpaste can decrease pain perceived at first hours after orthodontic appointment.

Registration and protocol: This trial was registered in Iranian Registry of Clinical Trials (IRCT2015010120523N1) at 16/04/2015.

Introduction:

Pain is one of the most important problems and concerns of patients, parents and clinicians during orthodontic treatment [1]. This pain can hinder patients from starting orthodontic treatment, make them to give up the treatment, and compromise effective plaque control [2, 3]. Prevention and management of

pain can increase patient's cooperation throughout orthodontic treatment [4, 5]. Although extensive research has been done about this issue, no standard method have yet introduced for pain relief and most of orthodontists traditionally prescribe analgesic drugs for pain management [3].

There are numerous methods for pain management during orthodontic treatment, including transcutaneous electrical nerve stimulation (TENS) [2, 6, 7], photobiomodulation [8–10], vibratory stimulation [11, 12], gum chewing or biting on plastic wafer [13, 14], and administration of non-steroidal anti-inflammatory drugs (NSAIDs) [15, 16]. It has been shown that intra-oral TENS is more effective that extra-oral TENS. So that, the procedure should be done in the clinic, decreasing patients' control on pain cycle after its emergence [17]. Photobiomodulation may reduce orthodontic pain in some patients. However, evidence regarding this issue is insufficient [4, 18, 19]. Vibration has been shown to reduce pain. Nevertheless, results of studies show controversy regarding its effectiveness [11, 12]. In spite of the fact that chewing gum and biting on plastic wafer is suitable for some patients, it seems ineffective in others [2, 7, 20]. In addition, they may bend archwires and increase appliance breakdown [21]. Systemic administration of NSAIDs and other analgesic drugs have some adverse effects. Uncontrolled usage can cause overdose [22]. In addition, drug interaction, mucous inflammation, gingival bleeding and interference in salivary secretion are some of the disadvantages of this method [23]. Besides, these drugs can negatively affect the rate of tooth movement. However, consumption of controlled doses during a short period minimizes these effects [4].

In the present study, benzocaine was added to toothpaste and was used to relieve orthodontic pain. Benzocaine is a local anesthetic drug and blocks voltage-dependent sodium channels and leads to reversible inhibition of impulses in nervous axons. Benzocaine is known as a low systemic toxicity drug and causes little drug interaction [4]. Benzocaine has previously been used in the form of muco-adhesive patch, chewing gum, gel and wax, and shown to be effective [1, 20, 24–26].

Toothpaste has numerous advantages as a drug carrier. As mentioned, pain perceived during orthodontic treatment can deteriorate plaque control. However, administration of toothpaste which contains analgesic drug can improve oral hygiene during the period. In addition, it has been shown that if analgesic drugs are pushed into gingival sulcus, it will become more effective [5]. The same would be true about benzocaine contained toothpaste which is pushed into gingival sulcus by toothbrush.

The purpose of the present study was to assess the effectiveness of benzocaine contained toothpaste on relieving pain perceived after orthodontic adjustment appointments.

Method And Material:

This was a cross-over, double blind randomized controlled trial conducted on 33 fixed orthodontic patients in the age range of 15–35 years old referred to orthodontic department of Shahid Beheshti University of Medical Sciences from January 2016 to June 2018. This trial was registered in Iranian Registry of Clinical Trials with the code of IRCT2015010120523N1 at 16/04/2015.

All of the patients and their representative authorities signed the informed consent. This study follows the Declaration of Helsinki on medical protocol and ethics. The research and medical ethics committee of Shahid Beheshti University of Medical Sciences approved the study protocol, as well.

Patient selection:

The inclusion criteria for sample selection were as followed:

1. Patients in leveling and alignment stage of orthodontic treatment whose only one arch (either arch) was bonded and had experienced orthodontic pain after previous appointment. The experienced pain in previous appointment should be equal or more than 50 according to Visual Analogue Scale (VAS) questionnaire.

2. Presence of 6–8 mm of space deficiency

3. Patient's acceptance to attend in the study

The exclusion criteria for sample selection include:

1. Current or previous history of severe renal or liver disease, or a history of hereditary methemoglobinemia

2. Presence of chronic pain and frequent consumption of analgesic drugs

3. Presence of acute or chronic pain in teeth or oral mucosa

4. Bonding of the opposite arch during the study period

Sample size was measured by Power and Sample size calculation software version 2.1.31 by considering standard deviation of 1.27 [24], 80% power, $\alpha = 0.05$ and to detect a clinically relevant difference of 1 in pain according to visual analog scale (VAS) questionnaire. This formula resulted to 26 subjects. Considering 20% lost to follow up, the number of subjects were rounded up to 33.

Study groups include:

1. 5% benzocaine contained toothpaste

2. Placebo toothpaste

3. Control group (with no toothpaste)

Producing benzocaine and placebo toothpastes:

Benzocaine contained and placebo toothpaste were manufactured in the Industrial laboratory of pharmacy school of Shahid Beheshti University of Medical Sciences. We chose a fluoridated toothpaste (Darugar 3, KAF Holding, Iran) which did not contain menthol flavor, since there are some evidences that

menthol can have an effect on sensory nerves [27]. The toothpastes were evacuated from the tubes into sterile dishes. The toothpaste was then levigated under room temperature with a mixer (Heidolph Instruments GmbH & Co.KG, Germany) with the rate of 500 rpm. For manufacturing benzocaine contained toothpaste, 5% benzocaine and 1% aspartame (Scientis Pharma SA, Switzerland) were added stage by stage to the tooth paste and mixed with the rate of 1000 rpm. The composition was mixed to produce homogenous texture.

Placebo toothpaste had the original composition of toothpaste and was only levigated to have the same appearance as benzocaine contained toothpaste.

The products were then dispensed in 50 gr tubes. The appearance of toothpaste and tubes were completely the same.

Randomization:

A random number was assigned to each tube. Randomization and sequence generation was done by random number generator in SPSS software by one author.

The study was conducted in a cross-over design. In other word, each patient experienced to be in each group in 3 following appointments. As designed, in the first stage of the study 11 patients were included in each group and these patients were exchangeably assigned to other groups sequentially. The randomized number of toothpastes and VAS questionnaires were written in opaque envelopes and were placed in three separate containers (each container included the numbers assigned to a separate group). The containers were numbered from 1 to 3. Afterwards, all of the compositions of numbers 1 to 3 were determined and were written in separate letters (1-2-3, 1-3-2, 2-1-3, 2-3-1, 3-2-1, 3-1-2). These letters were prepared in opaque envelopes and were placed in another container (sequence container). For randomized sequence and allocation concealment each patient draw envelopes from containers 1 to 3 to indicate the number of toothpastes and VAS questionnaires and an envelope from sequence container to indicate the sequence of the three groups. In each appointment the patient was given a benzocaine/ placebo or no toothpaste, a VAS questionnaire and a paper with the written instructions of the study design and oral hygiene instructions. Neither the patient nor the operator and outcome assessor were aware of the type of toothpastes. Wash out period was designed to be 4–6 weeks, meaning that after this period the group studies were changed according to our cross-over design.

Administration of toothpaste and marking the questionnaire:

The patients were instructed to use the toothpaste 3 times a day immediately after the appointment on first day and afterwards, after each meal, up to 3 days. The amount of toothpaste which should be placed on toothbrush was illustrated to them by a 1 cm line (containing approximately 0.05–0.1 gram of toothpaste). The exact method of brushing with cautions regarding the importance of not swallowing the paste was presented to each patient. The patients were not banned to consume analgesic but they were asked to mention the type of drug and time of administration. They were asked to brush a minimum of 5

minute each time and mark their pain in a VAS questionnaire at 2 hours, 6 hours, the night before sleep in the first day, at 10 am and 6 pm at day 2 and 3 and at 10 am at day 7. The questionnaire had a scale from 0 (indicating no pain) to 100 (the most severe pain ever experienced).

Statistical analysis: Statistical analysis was done with the aid of SPSS software version 23. Normal distribution of data was assessed by one sample Kolmogorov-Smirnov analysis. This analysis proved the normality ($P > 0.05$). So that, repeated measured ANOVA was used to compare groups and Bonferroni post hoc was used for comparing two-by-two analysis. Mean and standard deviation of pain in the groups were assessed in different time intervals. P value was set to be 0.05.

Results:

A total of 27 patients (23 females, 4 males) with mean age of 20.52 ± 5.8 (15–31) years old completed the study. The patients were recruited from January 2016 up to June 2018 and during this period, 6 patients (5 males, 1 female) were excluded due to consuming analgesic drugs or poor cooperation in using toothpaste or marking the questionnaire. Figure 1 shows the flow chart of the trial. Table 1 shows baseline demographic and clinical characteristics of patients.

Table 1
Baseline demographic and clinical characteristics of patients

Age range	
Range	15–31
Mean ± SD	20.52 ± 5.8
Sex	
Female	23
Male	4
Arch *	
Upper arch	15
Lower arch	12
*According to arch which was bonded first	

Table 2 shows total mean pain in all time intervals of three groups. The difference was not statistically significant (P value = 0.116).

Table 2
Total mean and standard deviation of pain in three groups.

Group	Mean	Standard deviation
Benzocaine	28.63	25.43
Placebo	31.31	22.09
Control	31.20	24.09

Figure 2 shows mean pain at different time intervals in three groups.

The results of Repeated measured ANOVA showed that in every time points in first day, subjects in benzocaine group experienced less pain that the other two groups and the difference was statistically significant at 2 hours ($T_1$2hrs) (P value 0.015).

Tables 3 to 5 show two-by-two comparison of pain in different time points in each group.

Table 3
Two-by-two comparison of pain in different time points in benzocaine group

First time point	Second time point	P value
2 hours	6 hours	0.670
	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	1.00
	6 pm day 3	1.00
	10 am day 7	0.432
6 hours	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	1.00
	6 pm day 3	1.00
	10 am day 7	0.087
First night before sleep	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	1.00
	6 pm day 3	1.00
	10 am day 7	0.076
10 am second day	6 pm day 2	1.00
	10 am day 3	0.408
	6 pm day 3	0.176
	10 am day 7	0.024*
6 pm second day	10 am day 3	1.00
	6 pm day 3	0.583
	10 am day 7	0.092

*statistically significant

First time point	Second time point	P value
10 am third day	6 pm day 3	1.00
	10 am day 7	0.302
6 pm third day	10 am day 7	0.743
*statistically significant		

Table 4
Two-by-two comparison of pain in different time points in placebo group

First time point	Second time point	P value
2 hours	6 hours	1.00
	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	0.025*
	6 pm day 3	0.002*
	10 am day 7	0.001*
6 hours	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	0.001*
	6 pm day 3	0.0001*
	10 am day 7	0.0001*
First night before sleep	10 am day 2	1.00
	6 pm day 2	1.00
	10 am day 3	0.107
	6 pm day 3	0.002*
	10 am day 7	0.001*
10 am second day	6 pm day 2	1.00
	10 am day 3	0.111
	6 pm day 3	0.001*
	10 am day 7	0.002*
6 pm second day	10 am day 3	1.00
	6 pm day 3	0.192
	10 am day 7	0.007*

*statistically significant

First time point	Second time point	P value
10 am third day	6 pm day 3	0.694
	10 am day 7	0.014*
6 pm third day	10 am day 7	0.116
*statistically significant		

Table 5
Two-by-two comparison of pain in different time points in control group

First time point	Second time point	P value
2 hours	6 hours	1.00
	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	0.075
	10 am day 3	1.00
	6 pm day 3	0.191
	10 am day 7	0.0001*
6 hours	First night before sleep	1.00
	10 am day 2	1.00
	6 pm day 2	0.544
	10 am day 3	1.00
	6 pm day 3	0.131
	10 am day 7	0.0001*
First night before sleep	10 am day 2	1.00
	6 pm day 2	0.396
	10 am day 3	1.00
	6 pm day 3	0.105
	10 am day 7	0.0001*
10 am second day	6 pm day 2	1.00
	10 am day 3	1.00
	6 pm day 3	0.746
	10 am day 7	0.002*
6 pm second day	10 am day 3	1.00
	6 pm day 3	1.00
	10 am day 7	0.006*

*statistically significant

First time point	Second time point	P value
10 am third day	6 pm day 3	1.00
	10 am day 7	0.006*
6 pm third day	10 am day 7	0.028*
*statistically significant		

All of the patients were examined in each appointment for possible adverse events. None of the patients reported any complications and no adverse reaction was observed in clinical examinations.

Discussion:

Pain is an undesirable experience after orthodontic appliance activation. The pain is local and ideally should be managed topically [23]. No standard method has yet proposed for reducing pain in orthodontic patients. In the present study, a novel method for drug delivery was evaluated for pain relief in orthodontics.

The result of the present study regarding benzocaine was in agreement with a previous study on benzocaine chewing gum, where the authors observed that benzocaine chewing gum was significantly more effective than placebo and ketoprofen chewing gum at 2 hours [20]. However, in both studies, the effect did not last. The first administration of both drug forms was immediately after orthodontic appointment. Considering the short half-time of benzocaine [28], it seems that the drug was useful in first hours. Although the effect was not permanent, this effect can break the pain cycle and help the patient to tolerate the pain more easily. As Cooper et al. stated, after pain onset, some factors can increase or decrease pain by amplifying and breaking the pain cycle [29]. Benzocaine can be a breaking factor.

Maximum pain in benzocaine group was at 10 am in day 2. This is comparable to the results of previous studies [30–32]. In a systematic review about the level of cytokines after orthodontic force, maximum level of IL-1β released 24 hours after force application and this increase was correlated with increased pain perception [33]. It has been shown that PGE_2 is the leading cause of pain in first hours. However, IL-1β is the cause of pain 1 day after force application [34]. In a meta-analysis about the effect of Ibuprofen in relieving orthodontic pain, the same effect was seen. In other words, Ibuprofen was effective in pain reduction in the first day, while ineffective at 24 hours.[35] This can be attributed to the mechanism of pain control by these two drugs, Ibuprofen and benzocaine. Benzocaine stabilizes the membrane of neurons reversibly and decreases sodium channel permeability, hence inhibiting neuron depolarization [36]. There are evidences that benzocaine can inhibit mechano-sensitive sodium channels in heart and gastero-intestinal tract.[37] There is not any evidence that sodium channels in PDL are similar to aforementioned channels. However, considering the mechanical sensitivity of PDL, this may come true. So that, benzocaine reliefs pain by changing sensory guidance and have little to do with the basic mechanism of pain, that is cytokine release, especially in hours in which cytokine levels are maximum.

The same may be true about the effect of Ibuprofen, which act by inhibiting arachidonic acid and prostaglandin formation, meaning that it has no effect on interleukins [23].

According to Fig. 1, after the first day, the pattern of change in pain is similar between the groups. This can be attributed to tachyphylaxis phenomenon, meaning that after repeated administration of anesthetic drug, the drug effect is reduced.[38] The cause of this phenomenon is unknown but some factors like edema, tissue hemorrhage, coagulation, changes in distribution of local anesthetic drug, hypernatremia and decrease in PH can play a role [39].

According to Tables 3 to 5, pain perceived in placebo and control groups show more fluctuation in amount in comparison with benzocaine group, which show more steady pain levels. Pain experienced at 10 am in second day was the maximum pain level in benzocaine group, and the level of pain in that time point was similar to those of the other two groups. However, this pain was not the maximum pain level in placebo and control groups.

Minimum level of pain was perceived at day 7 in all study groups. This finding was similar to those of other studies [16, 20, 40, 41]. Some authors have stated that at day 7, 42% of patients were still experiencing pain [32, 42]. The same was seen in our study where 49.4% of patients experienced pain at day 7.

An interesting finding of the present study was that, mean level of pain was somehow low. Maximum pain level did not reach to 45 according to VAS, even in placebo and control groups. This may be due to placebo effect [43], it seems that, behavioral factors, including reassurance and attention distraction are effective in managing orthodontic pain [44]. Giving a VAS questionnaire and explaining about pain, may reassure patient that his/her pain matters, even in control group. Interestingly, Pain level was not different between placebo and control groups. Cross-over design may have an assimilating effect on placebo effect of groups.

It is believed that in all patients, pain perceived at first appliance activation is more than the other appointments [15]. In other words, pain level is decreased after first appointment. Considering the fact that interventions was done in 3 sequentially appointments in cross over design, the questions are raised whether the results of interventions are comparable. However, in order to decrease this effect, we defined the sequence of interventions randomly.

In this study 5% benzocaine was added to toothpaste. This concentration was chosen to decrease the risk of overdoses and drug poisoning. In our previous studies we used 20% benzocaine in chewing gum [20]. However, the drug distribution with toothpaste carrier is different from those carried in chewing gum. So that, it was not safe and ethical to increase the concentration to 20%. More studies are needed to assess the safety of increasing the drug concentration.

Age and gender can affect pain expression [4]. However, results of studies regarding this issue show controversy [42, 45]. Cross-over design eliminated the probable effect of these factors on pain perception.

In the present study, the number of female subjects was more than male subjects (24 versus 10 in sampling). 5 male subjects versus 1 female subject were excluded further. This unequal distribution made it impossible to distinguish pain perception in females and males. This difference in distribution can be attributed to many factors including:

1. The number of females who experience pain in first appointment are more than males. The same was seen in Scheurer et al. and Kvam et al. studies [32, 46]. However, the findings were so controversial and some studies did not find any difference between genders regarding pain perception.[47]

2. The number of female orthodontic patients in orthodontic department was more than males.

3. More females were volunteer to attend in our study and they cooperated better during the study.

In present study, Visual Analogue Scale (VAS) was used as a measurement tool for pain assessment. VAS is an easily accessible, valid and reliable tool and because of its numerical and illustrative format, intercultural differences can not affect its validity [48]. However, its limited ability in differentiating sensory and afferent pain, may cause some errors [49]. So that, some authors have proposed measuring the level of chemical agents as a tool for pain perception [50]. Nevertheless, some authors believe that the level of these agents is not necessarily correlated with perceived pain [51]. More studies are needed to validate these methods.

Toothpaste is a novel carrier for drug delivery and is claimed to be able to reach the drug to local blood flow [52]. In addition, no adverse event was observed in the study subjects and toothpaste was a safe carrier for analgesic drugs. Patients' tolerance to benzocaine toothpaste was well.

Finally, it should be emphasized that pain has multifactorial and subjective nature and many factors can affect study findings, including age, gender, time of drug delivery, emotional status, cultural differences and previous experiences of patients [15]. In this study, we tried to decrease individual differences by a cross over design, randomization of groups and double blinded design.

Conclusion:

Benzocaine toothpaste was effective on pain relief in first hours after orthodontic appointment. Considering the short half-life of benzocaine, administering the drug immediately after orthodontic appointment is recommended. Benzocaine-contained toothpaste would be a novel and effective method for pain relief and oral hygiene, simultaneously.

Abbreviations

TENS: transcutaneous electrical nerve stimulation

NSAIDs: non-steroridal anti-inflammatory drugs

VAS: Visual Analogue Scale

Declarations

Ethics approval and consent to participate

The trial follows the declaration of Helsinki and was approved by Ethics Committee of Shahid Beheshti University of Medical Science. All patients or their representative authorities signed the informed consent.

Consent for publication

This manuscript does not contain any individual person's data.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was funded by Dental Research Center of Research Institute, Shahid Beheshti Medical University as a postgraduate thesis. Funding source did not have any role in designing, implementation, analysis, interpretation, and writing the manuscript.

Authors' contributions

LA: Conceptualization, Methodology, Writing- Review and Editing

SS: Investigation, Formal Analysis, Writing-Original Draft

SS: Investigation, Writing- Review and Editing

SAM: Methodology, Visualization

Acknowledgements

Not applicable

References

1. Kluemper GT, Hiser DG, Rayens MK, Jay MJ. Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. Am J Orthod Dentofac Orthop. 2002;122:359–

65.
2. Hwang JY, Tee CH, Huang AT, Taft L. Effectiveness of thera-bite wafers in reducing pain. J Clin Orthod. 1994;28:291–2.
3. Krukemeyer AM, Arruda AO, Inglehart MR. Pain and orthodontic treatment. Angle Orthod. 2009;79:1175–81.
4. Krishnan V. Orthodontic pain: from causes to management—a review. Eur J Orthod. 2007;29:170–9.
5. Keim RG. Managing orthodontic pain. J Clin Orthod. 2004;38:641–2.
6. Dogra N, Head S, Grover S. TENS in management of orthodontic pain: A review. ~ 34 ~ Int J Appl Dent Sci. 2020;6:34–6. .
7. White LW. Pain and cooperation in orthodontic treatment. J Clin Orthod. 1984;18:572–5.
8. Sfondrini MF, Vitale M, Pinheiro ALB, Gandini P, Sorrentino L, Iarussi UM, et al. Photobiomodulation and Pain Reduction in Patients Requiring Orthodontic Band Application: Randomized Clinical Trial. Biomed Res Int. 2020;2020.
9. Cronshaw M, Parker S, Anagnostaki E, Lynch E. Systematic Review of Orthodontic Treatment Management with Photobiomodulation Therapy. Photobiomodulation, Photomedicine, Laser Surg. 2019;37:862–8.
10. Eslamian L, Borzabadi-Farahani A, Hassanzadeh-Azhiri A, Badiee MR, Fekrazad R. The effect of 810-nm low-level laser therapy on pain caused by orthodontic elastomeric separators. Lasers Med Sci. 2014;29:559–64.
11. Katchooi M, Cohanim B, Tai S, Bayirli B, Spiekerman C, Huang G. Effect of supplemental vibration on orthodontic treatment with aligners: A randomized trial. Am J Orthod Dentofac Orthop. 2018;153:336–46.
12. Celebi F, Turk T, Bicakci AA. Effects of low-level laser therapy and mechanical vibration on orthodontic pain caused by initial archwire. Am J Orthod Dentofac Orthop. 2019;156:87–93.
13. Ireland AJ, Ellis P, Jordan A, Bradley R, Ewings P, Atack 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 Dentofac Orthop. 2016;150:220–7.
14. 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 Craniofacial Res. 2012;15:178–87.
15. Ozsoy OP, Karaman AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain (Angle Orthodontist (2005) 75,5, (791–796)). Angle Orthod. 2008;78:976.
16. 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 Dentofac Orthop. 2001;120:20–7.
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;90:132–8.

18. Deana NF, Zaror C, Sandoval P, Alves N. Effectiveness of Low-Level Laser Therapy in Reducing Orthodontic Pain: A Systematic Review and Meta-Analysis. Pain Res Manag. 2017;2017.
19. Li FJ, Zhang JY, Zeng XT, Guo Y. Low-level laser therapy for orthodontic pain: a systematic review. Lasers Med Sci. 2015;30:1789–803.
20. Eslamian L, Youssefinia S, Ameli N. Efficacy of Ketoprofen and Benzocaine Chewing Gums for Reducing Orthodontic Pain. J Islam Dent Assoc. 2014;26:218–24. http://www.jidai.ir/browse.php?a_code=A-10-1-796&slc_lang=en&sid=1.
21. Eslamian L, Kianipour A, Mortazavi SAR. The analgesic efficacy of 5% naproxen gel for pain associated with orthodontic separator placement: a randomized double-blind controlled trial. Anesthesiol pain Med. 2017;7.
22. Matusiak R, Harley KE. Paracetamol overdose in a teenager following placement of a fixed appliance. Dent Update. 2009;36:33–5.
23. Krasny M, Zadurska M, Cessak G, Fiedor P. Analysis of effect of non-steroidal anti-inflammatory drugs on teeth and oral tissues during orthodontic treatment. Report based on literature review. Acta Pol Pharm - Drug Res. 2013;70:573–7.
24. Eslamian L, Borzabadi-Farahani A, Edini HZ, Badiee MR, Lynch E, Mortazavi A. The analgesic effect of benzocaine mucoadhesive patches on orthodontic pain caused by elastomeric separators, a preliminary study. Acta Odontol Scand. 2013;71:1168–73.
25. Eslamian L, Gholami H, Mortazavi SAR, Soheilifar S. Effect of 5% benzocaine gel on relieving pain caused by fixed orthodontic appliance activation. A double-blind randomized controlled trial. Orthod Craniofacial Res. 2016;19.
26. Eslamian L, Borzabadi-Farahani A, Gholami H. The effect of benzocaine and ketoprofen gels on pain during fixed orthodontic appliance treatment: a randomised, double-blind, crossover trial. Aust Orthod J. 2016;32:64.
27. Naganawa T, Baad-Hansen L, Ando T, Svensson P. Influence of topical application of capsaicin, menthol and local anesthetics on intraoral somatosensory sensitivity in healthy subjects: temporal and spatial aspects. Exp Brain Res. 2015;233:1189–99.
28. Khair-ul-Bariyah S, Arshad M, Ali M, Din MI, Sharif A, Ahmed E. Benzocaine: Review on a Drug with Unfold Potential. Mini Rev Med Chem. 2020;20:3–11.
29. Cooper RG, Booker CK, Spanswick CC. What is pain management, and what is its relevance to the rheumatologist? Rheumatology. 2003;42:1133–7.
30. Ngan P, Kess B, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment. Am J Orthod Dentofac Orthop. 1989;96:47–53.
31. Firestone AR, Scheurer PA, Bürgin WB. Patients' anticipation of pain and pain-related side effects, and their perception of pain as a result of orthodontic treatment with fixed appliances. Eur J Orthod. 1999;21:387–96.
32. 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.

33. Kapoor P, Monga N, Kharbanda OP, Kapila S, Miglani R, Moganty R. Effect of orthodontic forces on levels of enzymes in gingival crevicular fluid (GCF): A systematic review. Dental Press J Orthod. 2019;24:40.e1-40.e22.
34. Giannopoulou C, Dudic A, Kiliaridis S. Pain Discomfort and Crevicular Fluid Changes Induced by Orthodontic Elastic Separators in Children. J Pain. 2006;7:367–76.
35. Angelopoulou M V., Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: A meta-analysis. Orthod Craniofacial Res. 2012;15:71–83.
36. National Center for Biotechnology Information. PubChem Compound Summary for CID 4946, Propranolol. 2021. https://pubchem.ncbi.nlm.nih.gov/compound/Propranolol. Accessed 8 Jun 2021.
37. Beyder A, Strege PR, Bernard C, Farrugia G. Membrane permeable local anesthetics modulate NaV1.5 mechanosensitivity. Channels. 2012;6:308–16.
38. Vandermeulen E. [Pain perception, mechanisms of action of local anesthetics and possible causes of failure]. Rev Belge Med Dent (1984). 2000;55:29–40. http://www.ncbi.nlm.nih.gov/pubmed/11039281.
39. Kottenberg-Assenmacher E, Peters J. Mechanisms of tachyphylaxia in regional anesthesia of long duration. AINS - Anästhesiologie, Intensivmed Notfallmedizin, Schmerztherapie. 1999;34:733–42.
40. Wilson S, Ngan P, Kess B. Time course of the discomfort in young patients undergoing orthodontic treatment. Pediatr Dent. 1989;11:107–10.
41. Steen SL, Southard KA, Alan S, Logan HL, Jakobsen JR. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am J Orthod Dentofac Orthop. 2000;118:629–35.
42. Bergius M, Berggren U, Kiliaridis S. Experience of pain during an orthodontic procedure. Eur J Oral Sci. 2002;110:92–8.
43. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 2008;59:565–90.
44. Long H, Wang Y, Jian F, Liao L-N, Yang X, Lai W-L. Current advances in orthodontic pain. Int J Oral Sci. 2016;8:67–75.
45. Farias RD, Closs LQ, Miguens Jr SAQ. Evaluation of the use of low-level laser therapy in pain control in orthodontic patients: A randomized split-mouth clinical trial. Angle Orthod. 2016;86:193–8.
46. Kvam E, Bondevik O, Gjerdet NR. Traumatic ulcers and pain in adults during orthodontic treatment. Community Dent Oral Epidemiol. 1989;17:154–7.
47. Jones M, Chan C. The pain and discomfort experienced during orthodntic treatment: A randomized controlled clinical trial of two intial aligning arch wires. Am J Orthod Dentofac Orthop. 1992;102:373–81.
48. Langley GB, Sheppeard H. The visual analogue scale: its use in pain measurement. Rheumatol Int. 1985;5:145–8.

49. Duncan GH, Bushnell MC, Lavigne GJ. Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. Pain. 1989;37:295–303.
50. Horinuki E, Yamamoto K, Shimizu N, Koshikawa N, Kobayashi M. Sequential changes in cortical excitation during orthodontic treatment. J Dent Res. 2016;95:897–905.
51. Gameiro GH, Schultz C, Trein MP, Mundstock KS, Weidlich P, Goularte JF. Association among pain, masticatory performance, and proinflammatory cytokines in crevicular fluid during orthodontic treatment. Am J Orthod Dentofac Orthop. 2015;148:967–73.
52. Moskowitz D. Delivery of drugs to the bloodstream in toothpaste. 2005.

Figures

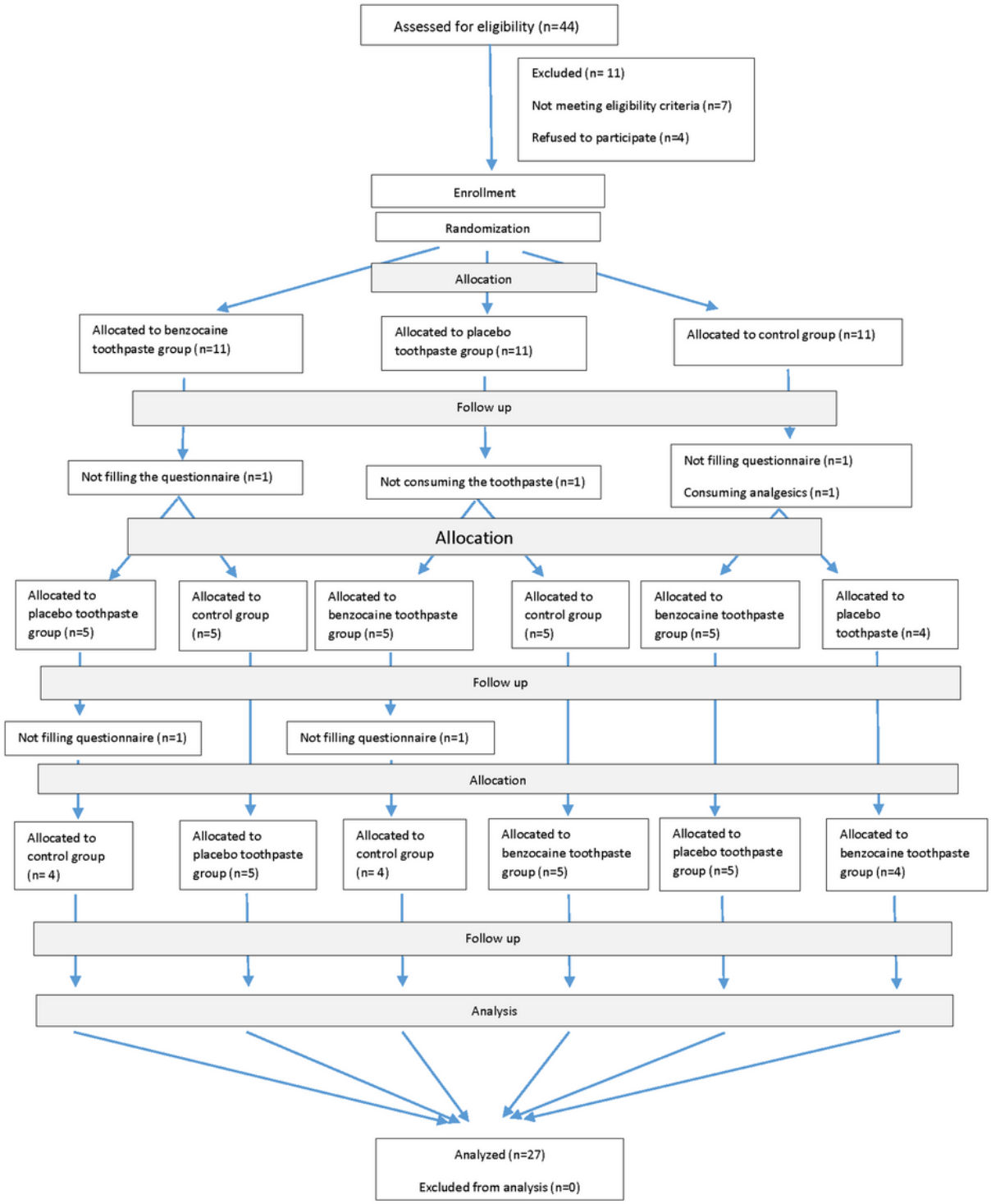

Figure 1

Flow chart of the trial patient recruitment

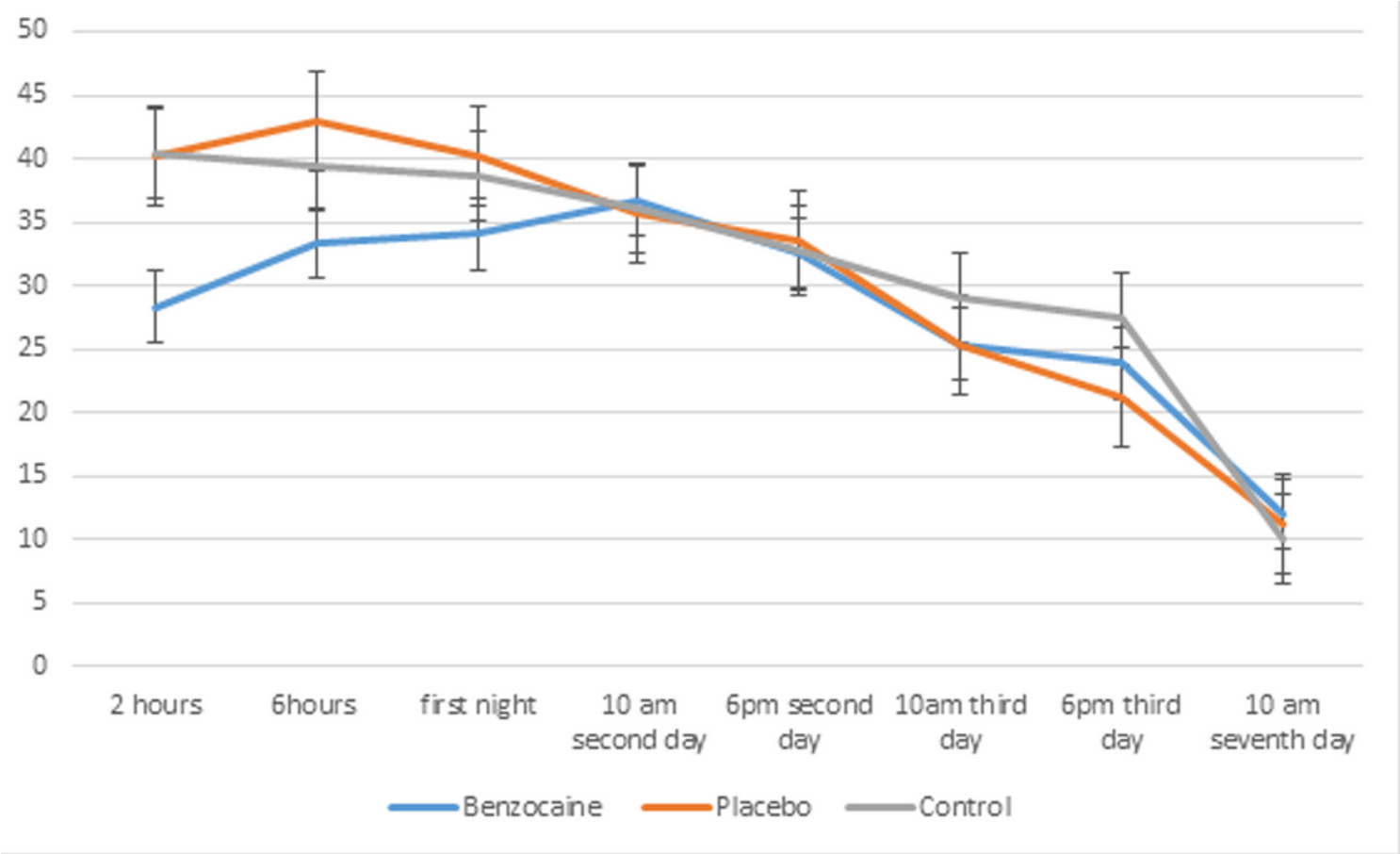

Figure 2

Comparison of pain in 8 different time points in three groups.