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Abstract

Purpose: This study aimed to compare the effect of benzocaine and menthol patches on pain alleviation following elastomeric separator placement.

Patients and Methods: This triple-blind split-mouth trial was conducted on healthy 14-25 years old patients of orthodontic department. Eligibility criteria included presence of second premolar, first and second molars in both sides of the mandible, no chronic pain in oral cavity, or chronic consumption of analgesic drugs. Elastomeric separators were placed mesial and distal of first mandibular molars and patients were randomized into two groups: 1) menthol/ placebo patches, 2) benzocaine/ placebo patches. The mucosal patches were placed randomly on the buccal area of mandibular first molars on both sides. Main outcome was pain level reported by patients on the Visual Analogue Scale (VAS) in seven-time intervals in three following days. Data were analyzed by linear mixed model. P-value was set to be 0.05.

Results: Sixty-four patients were randomized in a 1:1 ratio with no loss to follow-up. Both benzocaine and menthol patches significantly reduced mean pain level compared to placebo patch (P< 0.001). Benzocaine patch had more analgesic effect; however, the difference was not statistically significant (P=0.115). Time interval had a significant effect on recorded pain except the first time interval. Age and gender had no significant effect on pain. No adverse event was reported in patients.

Conclusions: Both benzocaine and menthol patches were effective in alleviating pain. Therefore, they can be recommended to be used for reducing pain following orthodontic elastomeric separator placement.

Keywords

Pain; Orthodontics; Benzocaine; Menthol; Visual Analog Scale

Authors

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ORIGINAL ARTICLE

Evaluation of Pain-relieving Effect of Menthol and Benzocaine Patches in Orthodontic Patients: A Triple-blind Randomized Controlled Trial

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ABSTRACT

Purpose: **This study aimed to compare the effect of benzocaine and menthol patches on pain alleviation following elastomeric separator placement.**

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Conclusions: **Both benzocaine and menthol patches were effective in alleviating pain. Therefore, they can be recommended to be used for reducing pain following orthodontic elastomeric separator placement.** ***Taiwanese Journal of Orthodontics 2022;34(2):81−89***

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INTRODUCTION

Patients undergoing orthodontic treatment experience various degrees of pain after activating orthodontic appliances and placing interproximal separators, especially within the first 4 days.[1] Using interproximal separators between first molars and second premolars is mandatory to create enough space for placing orthodontic bands. Orthodontic pain prevents correct plaque control and affects overall patient's satisfaction with the treatment. Previous studies have shown that orthodontic pain can produce highly significant changes in brain structure and

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function. Therefore, the orthodontist can increase patient cooperation with preventing and controlling pain.[2−4]

A variety of approaches have been introduced to reduce pain during orthodontic treatment: oral NSAIDs, local use of anesthetic gels, chewing gum or biting wafer, laser, and vibratory stimulation.[5−7] However, none of these methods have been proved to be the right solution.

Benzocaine is a local anesthetic drug utilized in dentistry and minor surgeries. It has no negative effect on tooth movement and causes minimal systemic side effects. In some studies, benzocaine has been applied for relieving orthodontic treatment pain and reducing mucosal irritation.[8−12]

Menthol, an extracted material from mint (*Mentha piperita*), is a local anesthetic agent that has been used as menthol patch and gel in treating painful conditions such as allodynia, migraine, musculoskeletal pain, neuropathy, and sports injuries.[13−15]

Considering the fact that placing separator is carried out in the commencement of treatment and is usually accompanied by pain, reducing pain in this step can be radically influential in motivating patients and lowering their stress for orthodontic treatment. Side effects of systemic drugs made present authors search for a modern and accurate method of controlling pain introducing a local anti-pain drug to reduce pain which is less irritating for patients. The purpose of this study was to compare the effect of benzocaine and menthol patches to reduce pain after placement of elastomeric separators.

MATERIALS AND METHODS

This randomized split-mouth controlled triple-blind clinical trial with a 1:1 allocation ratio was carried out using split-mouth design on 64 patients (25 males, 39 females), 14−25 years old, in the orthodontic department of dental school of Hamedan University of Medical Sciences from 2017 to 2019.

The sample size was calculated by PWR package in R-software according to the finding of Eslamian et al.[9] In this research, the effect of benzocaine and placebo mucoadhesive patches on pain caused by elastomeric separators were compared. Perceived pain at 72 h were 0.97 ± 0.85 and 1.67 ± 0.92 in benzocaine and placebo patches, respectively. Expected mean and standard deviation were calculated from the data reported by this article. Considering 5% alpha error, 80% statistical power, standard deviation of 1.27, 20% lost to follow up, and to find a difference of 0.7 in mean pain, a total sample size of 64 was measured (32 in each group).

The trial follows the declaration of Helsinki and was approved by Ethics Committee of Hamedan University of Medical Sciences (IR.UMSHA.REC.1395.225) and registered at Iran Registry of Clinical trials with code of (IRCT2016080129155N1).

The inclusion criteria were as follows:

1. No pain in the region of mouth at the beginning of the study
2. Presence of moderate crowding (4−8 mm) in mandibular arch
3. Presence of first molars, second molars, and second premolars of mandible with tight interproximal contacts.

The exclusion criteria were as follows:

1. Pregnancy
2. History of liver or kidney disease
3. History of allergy to local anesthetic drugs
4. History of methemoglobinemia
5. Chronic consumption of NSAIDS, sedatives, or other analgesic drugs

Study protocol was explained to patients and informed consent was obtained from patients or their representative authorities.

Patients were randomly categorized into two groups. Stratified randomization according to age and gender was done with the aid of www.sealedenvelope.com. The samples were divided into subgroups according to age (14−18 years old versus 18−25 years old) and gender (female versus male). The samples were chosen randomly from these subgroups. A list of numbers was prepared and written in opaque envelopes. Patients were asked to take an envelope from a container. The number in the envelop defined the assigned group of the patient (benzocaine/placebo or menthol/placebo) and the side of patch placement (right or left). Allocation concealment, sequence generation, and patient enrollment were done by three authors (SS, FD, SS, respectively).

The study was designed to be triple-blind. Benzocaine, menthol, and placebo patches had a completely similar appearance. The patients, the operator, and the outcome assessor were not aware of the type of patch on each side.

Elastomeric separators (Dentarum, Springen, Germany) were placed in mesial and distal contacts of first mandibular molars. The first group randomly used menthol patch on one side and placebo patch on the other side of lower arch. The second group used benzocaine and placebo patches, randomly on each side of lower arch. Placement

method was taught to patients so that they place half of the patch on tooth and half over the attached gingiva of mandibular permanent first molar (Figure 1). The patches remained in place until they resolved. The patients were asked to use the first patch immediately after placing separator, and if needed, repeat this process every 6 h for three days. The patches had the size of 1.5 cm * 1.5 cm and were produced under the supervision of a pharmaceutical consultant. Benzocaine patch contained 20 mg benzocaine (equal to one puff of 20% benzocaine spray),[9] and menthol patch contained 20 mg menthol. In addition, the patches consisted of dichloromethane, polyvinyl pyrrolidone, propylene glycol, ethanol, hydroxyl propylene methylcellulose, and aspartame. The patients were asked to avoid consuming any analgesic drugs during the study protocol and if unavoidable, they could use acetaminophen 325 mg and should mention this in the questionnaire. They were instructed to fill out a questionnaire made by visual analogue scale, involving 0 to 10 scores for level of pain in time intervals of 2, 6, 12, 24, 36, 48, and 72 h after placing interproximal separators. These time intervals were provided in previous studies and involve recorded times for maximum intensity of pain.[16] Taking analgesic drugs during study period (except for 325 mg Acetaminophen which was mentioned in the questionnaire), patients' incompliance in filling out the questionnaire or self-declaration of not consuming the patches, as well as, separator coming out during study period led to exclusion of the patient after trial commencement.

Figure 1. A patch placed on lower first mandibular molar. Half of the patch is on the gingiva. The saliva and the slightly sticky nature of the patches, caused the initial stability of the patch over the tooth and gingiva.

Data was analyzed by SPSS software, version 23 (IBM, Armonk, NY). Means and standard deviation of pain were measured at different time intervals in each group. Linear Mixed Model (LMM) analyses were performed to investigate the effect of patch type, time interval, age, and gender on perceived pain. In this analysis, participant was treated as a random effect to group the data per participant. This means that the same participant was measured multiple times. In other words, the intercept is not constant and is a random variable, i.e. the intercept varies between persons. Person characteristics, such as age (in two groups of less than 18 years old and more than 18 years old) and gender, were also added to control for these variables. Data of placebo patches in both groups of patients were pooled as the control group. In this analysis, for each variable, a factor was considered as reference category and the other factors were compared to it. We considered the control group, male gender, age over 18 years old, and 7th time interval as reference categories. The statistically significant difference was set at $P < 0.05$.

The effect of type of patches on perceived pain were compared with Bonferroni adjustment for multiple comparisons to account for type 1 error. Since we had three comparisons, significance level would be divided by three; i.e. $0.05/3 = 0.016$. This was automatically addressed in measured P-value of analysis by SPSS software.

RESULTS

Seventy-three orthodontic patients were enrolled in the study from April 2019 up to June 2020, nine of the patients were excluded according to eligibility criteria. Figure 2 shows the process of participant selection.

None of the patients reported consumption of Acetaminophen or other analgesics. Using of patches had no significant adverse effect or complication. None of the separators came out during study. All of the patients applied the patches as instructed and filled out the questionnaire.

Demographic data of participants are shown in Table 1. Gender and age distributions were similar in all groups. Chi-square test showed no significant statistical difference in age and gender between groups (P value < 0.34 and P value < 0.61, respectively).

Results of descriptive analysis, including mean, standard deviation, and 95% confidence interval of pain in studied groups at different time intervals are shown in Table 2, Figure 3A and B compare the effect of menthol/placebo patches and benzocaine/placebo patches, respectively.

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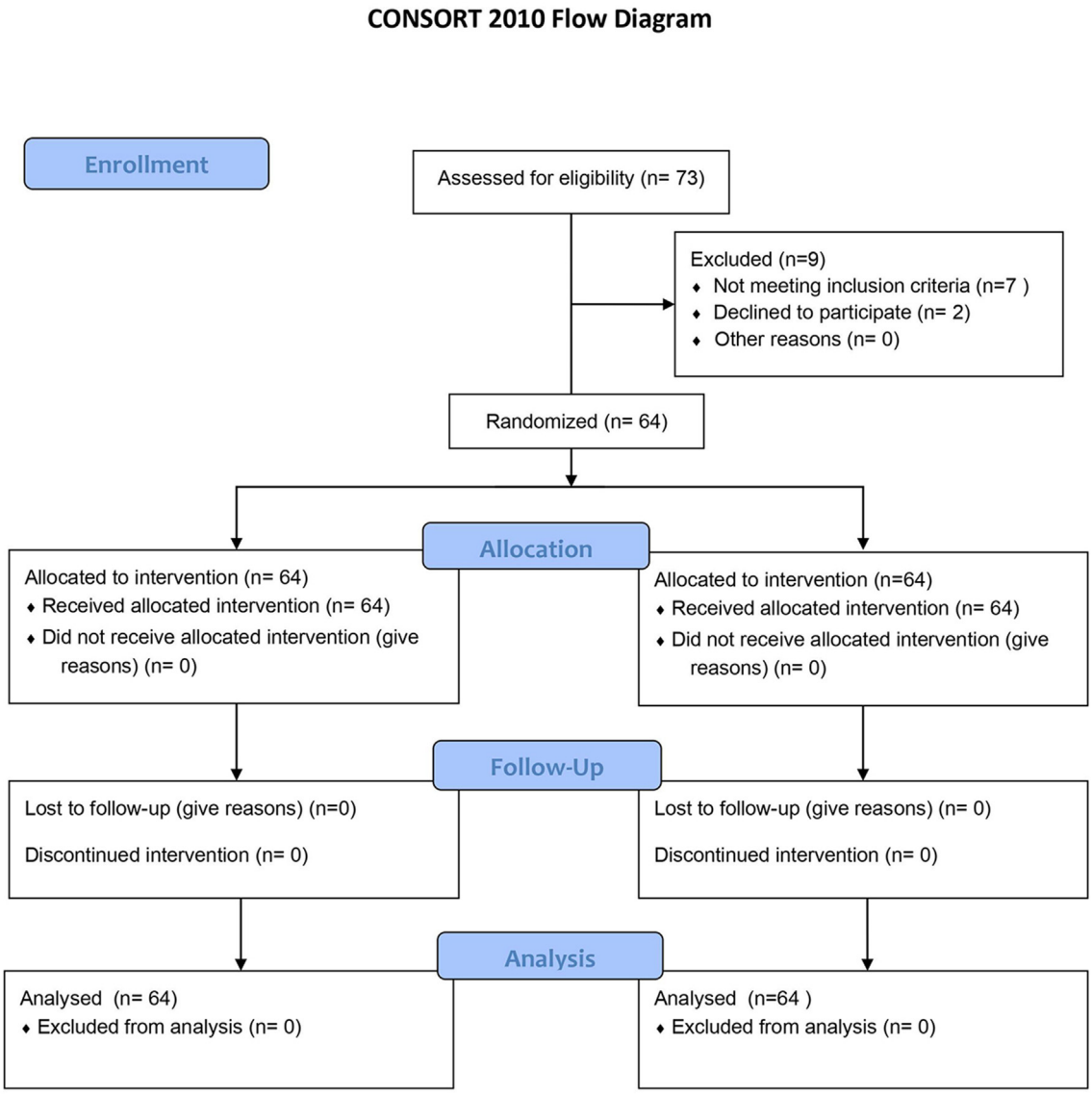

Figure 2. Flow diagram of trial participant recruitment.

Table 3 shows the results of linear mixed model. In this analysis, both placebo groups were pooled and a single control group was considered. Figure 3C shows the trend of changes in different time intervals in three studied groups.

In Figure 3, each factor is compared to its reference category. Placebo group was considered as reference category to evaluate the effect of patch type on perceived pain. The perceived pain was less in both menthol and benzocaine groups compared to placebo group (reference category) and the differences were statistically significant ($p < 0.001$, $P < 0.001$, respectively). Although benzocaine patch caused more analgesic effect than menthol patch, according to adjustment for multiple comparison Bonferroni analysis the difference between these two groups was not statistically significant ($P = 0.115$). Mean recorded pain in menthol, benzocaine and control groups were 1.86 (standard error = 0.18), 1.47 (standard error = 0.18), 2.75 (standard error = 0.16), respectively (Tables 4 and 5).

Seventh time interval was considered as reference category to assess the effect of time intervals.

Table 1. Demographic data of study participants.

Group	14–18 years old		18–25 years old		Age (Mean ± SD)
	Female	Male	Female	Male	
Menthol-Placebo	10	9	9	4	18.97 ± 2.94
Benzocain-Placebo	11	8	6	7	17.87 ± 3.74

Table 2. Mean and standard deviation of perceived pain in study groups at different follow up times.

Time interval	Mean pain± SD 95% CI[a] Lower bound-Upper bound		Mean pain± SD 95% CI[a] Lower bound-Upper bound	
	Menthol	Placebo	Benzocaine	Placebo
1	1.3 ± 1.35 0.54_ 1.52	0.97 ± 0.97 0.62_ 1.32	0.97 ± 0.78 0.69_ 1.25	1.69 ± 0.99 1.33_ 2.05
2	2.06 ± 1.34 1.58_ 2.55	4 ± 1.83 3.34_ 4.66	1.5 ± 0.72 1.24_ 1.75	3.43 ± 1.60 2.86_ 4.02
3	2.69 ± 1.84 2.02_ 3.35	4.59 ± 2.11 3.83_ 5.35	2.09 ± 1.30 1.62_ 2.56	3.81 ± 1.71 3.19_ 4.43
4	2.31 ± 2.16 1.53_ 3.09	3.66 ± 2.36 2.80_ 4.51	2.06 ± 2.06 1.32_ 2.81	3.72 ± 2.08 2.97_ 4.47
5	2.47 ± 2.38 1.61_ 3.33	2.87 ± 2.31 2.04- 3.71	1.25 ± 1.92 0.56_ 1.94	2.69 ± 2.25 1.88_ 3.50
6	2.03 ± 2.21 1.23_ 2.83	2.47 ± 2.05 1.73_ 3.21	0.94 ± 1.7 0.32_ 1.55	1.66 ± 2.12 0.89_ 2.42
7	1.37 ± 1.68 0.77_ 1.98	1.87 ± 1.91 1.18_ 2.56	0.81 ± 1.65 0.21_ 1.41	1.37 ± 1.96 0.67_ 2.08

[a] Confidence interval.

Perceived pain in the second, third, fourth, fifth, and sixth time intervals showed statistically significant difference compared to the seventh time interval (reference category) ($P < 0.001$). In all three groups, maximum pain was recorded at the third time interval (12 h after placing separator). Pain was not significantly different between the first and the seventh time intervals.

Linear mixed model showed that gender and age did not have a significant effect on changes in perceived pain.

DISCUSSION

The present study evaluated the effect of benzocaine and menthol patches on pain reduction using VAS at 2, 6, 12, 24, 36, and 72 h after orthodontics elastomeric separator placement. The results showed that benzocaine group had statistically significant lower pain score compared to the placebo group. Anesthetic effect with 20% benzocaine usually starts within 30 s and lasts for up to 15 min. Topical application of this agent is effective in inhibition of pain in superficial tissues.[17] In contrast to other local anesthetic drugs, benzocaine can act in environments with low pH.[18] This can explain why the drug is effective in low pH environment of orthodontically moved teeth. In the present study, benzocaine patches with 20% concentration were applied on the tooth and gingiva, covering the gingival sulcus. It is possible that benzocaine can be absorbed by PDL via gingival crevicular fluid. Since the origin of orthodontic pain is PDL, this topical application may be effective in pain management. Furthermore, mucosal patches increased the time that the drug is in contact with the tissue.[19] Although the duration of anesthetic effect of benzocaine is short, it is possible that the agent is able to break the pain cycle and thus, be effective in consistent pain reduction. Cooper et al. have observed that after commencement of pain, many factors (i.e psychologic and physiologic) can exacerbate pain perception. Breaking this pain cycle can avoid increased pain perception.[20] This result is similar to Eslamian et al.[9] In her study with split-mouth method, the effect of benzocaine and placebo patches in reducing pain following elastomeric separator placement was compared. She found that less pain was experienced in the Benzocaine side.[9] In the study of Hersh et al., mucosal patch with 12 mg benzocaine was applied to decrease instantaneous dental pains and it was found that more percentage of patients reported pain relief with benzocaine patch than placebo.[21]

It was found that applying menthol patches resulted in statistically significant lower pain scores than placebo. These findings suggest that using benzocaine and menthol patches are efficient pharmaceutical methods to reduce orthodontic pain resulted from placement of elastomeric separators. Benzocaine patch had more anti-pain effect than menthol patch. However, the difference was not statistically significant. Menthol is an agonist of Transient Receptor Potential Melastatin-8 (TRMP8) receptor, known as menthol receptor. These receptors are found in thermosensitive neurons and they became sensitized due to exposure to menthol, leading to coolness perception and inhibition of pain impulse conduction. Menthol may cause blockage of sodium channels.[14,15] Evidence regarding its vasoactive effect is contradictory, some support its vasodilation and increased blood flow effect,[15] and others claim that menthol causes reduced blood flow.[22] Cooling effect, sodium channel blockage, and possible vasodilation mechanisms can explain its potential in decreasing orthodontic pain. Sodium channel blockage by menthol is weak.[15] This can explain weaker analgesic effect of menthol compared to benzocaine. Although the anti-pain effect of menthol is proved in many studies,[13−15,23] no research is available with respect to applying menthol for reducing pain from orthodontic treatment. Naganawa et al. evaluated topical application of capsaicin, menthol, and local anesthetics on intraoral somatosensory sensitivity. They applied these drugs on the gingiva and used mechanical and thermal stimuli on that area. They found no significant difference in pain scores between menthol and control groups.[24] However, in

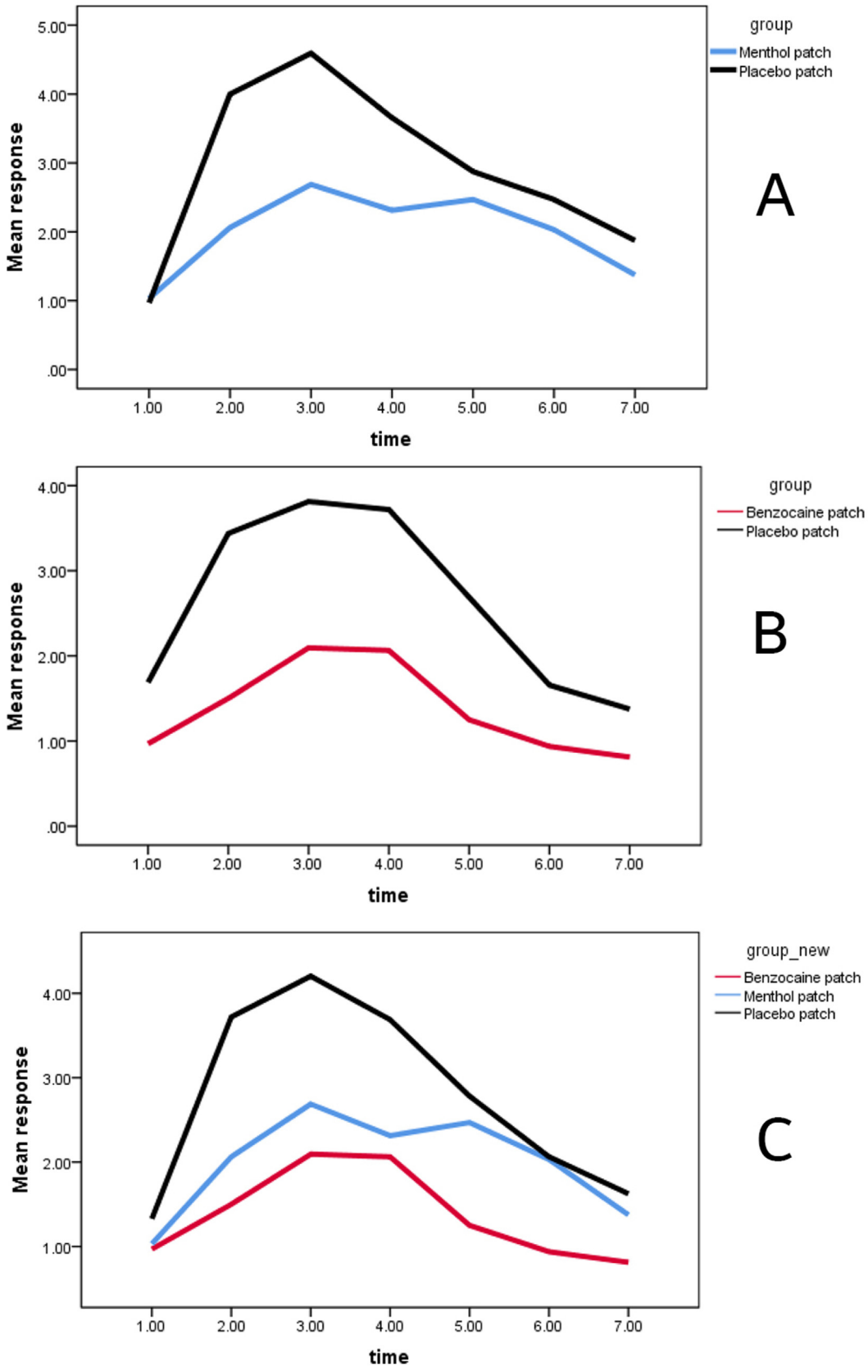

Figure 3. Line graph indicating mean level of pain (mean pain) in study groups at all time intervals (horizontal axis: 1: 2 h, 2: 6 h, 3: 12 h, 4: 24 h, 5: 36 h, 6: 48 h, 7: 72 h). A. Menthol and placebo patches; B. Benzocaine and placebo patches; C, Menthol, benzocaine, and placebo patches.

Table 3. Results of linear mixed model on effect of patch type, time interval, age and gender effect on recorded pain.

Parameter	Mean difference	Standard error	P value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	1.78	0.30	0.001	1.17	2.38
Menthol patch	−0.89	0.14	0.001	−1.16	−0.62
Benzocaine patch	−1.28	0.14	0.001	−1.55	−1.01
Control patch (reference category)	–	–	–	–	–
Time 1	−0.19	0.19	0.298	−0.56	0.17
Time 2	1.39	0.19	0.001	1.02	1.76
Time 3	1.94	0.19	0.001	1.57	2.30
Time 4	1.58	0.19	0.001	1.21	1.95
Time 5	0.96	0.19	0.001	0.59	1.33
Time 6	0.41	0.19	0.027	0.05	0.78
Time 7 (reference category)	–	–	–	–	–
Age (<18 years old)	0.24	0.29	0.412	−0.33	0.81
Age (>18 years old) (reference category)	–	–	–	–	–
Female	−0.02	0.28	0.927	−0.57	0.52
Male (reference category)	–	–	–	–	–

the present study, type of pain inducing stimulus (tooth movement) and design of the study (split-mouth) are different from Naganawa et al.'s research.

Considering mean of pain in two elastomeric separator groups, the results indicated that pain increases following placing separator and reaches to its maximum in the third time interval (12 h after placing separator) and finally falls down. In the seventh time interval (third day), some patients still reported pain. Studying flow of pain showed that pain from elastomeric separator is not linear and followed a quadratic pattern (Figure 3). When the separator is placed, the vessels on the compression side are squeezed and ischemia occurs, causing anaerobic respiration and acidosis. Acid-sensing ion channel 3 (ASIC 3) is an ion channel receptor in periodontal tissue and recognizes both acidity changes and mechanical forces and transduces them to painful signals. When the force is kept minimal, the mechanosensation role is not significant. So that, early hours following force application, perceived pain is minimal. Local inflammation occurs in 12 h. This phenomenon explains the fact that most patients experience the maximal pain level at approximately 12 h.[25]

Similar to this finding, Sandhu et al. showed that pain starts almost one hour following placing separator, and it follows a non-linear form in a quadratic shape. However, the maximum pain in this study was in the morning of the first day or 24 h after placing separator.[26] Maximum level of pain in Eslamian et al. study was 24 h after placing separator.[9] According to Giannopoulou et al., level of pain increases from one to 24 h following placing separator.[27] The multifactorial and subjective nature of pain, different age ranges of the participants, and using different types of separators could influence the results and this could be the reason for difference in the time of maximum pain in different studies.

Pain assessment was done by Visual Analogue Scale (VAS). VAS is a non-verbal, valid, reliable, reproducible, easily accessible, and sensitive method. In addition, because of its illustrative platform and minimal dependence on language, results of different studies in various cultures can be compared easily.[28] Although being precise, some authors stated that its unidirectional, linear nature leads to errors in differentiating between sensory and afferent (unpleasant) aspects of pain.[29] Thus, some researchers believe that measuring chemical messengers of pain is a better method. Interleukin-1β is the primary mediator to regulate bone remodeling in response to orthodontic forces and plays an important role in responding to

Table 4. Estimated marginal means of recorded pain based on the linear mixed model.

	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Benzocaine patch	1.47	0.182	1.110	1.831
Menthol patch	1.86	0.183	1.500	2.224
Control patch	2.75	0.155	2.443	3.062

Table 5. Pairwise comparison of patches based on Bonferroni adjustment for comparisons.

First groups	Second group	Mean difference	Standard error	P value
Benzocaine patch	Menthol patch	−0.392	0.189	0.115
	Placebo patch	−1.289	0.189	0.0001
Menthol patch	Placebo patch	−0.899	0.138	0.0001

orthodontic pains. Previous studies showed that concentration of IL-1β promoted after one hour of applying force, the maximum of IL-1β was seen after 24 h, and it reduced to its normal level after one week.[30,31] So that, level of this chemical agent can act as a measure of pain intensity. However, Gameiro et al., have stated that level of IL-1β is not necessarily correlated with intensity of experience pain.[32] Therefore, more studies are required to evaluate the precise correlation between level of IL-1β and subjective pain scores.

Multiple factors can affect pain perception, including age and gender. Some authors have reported that females and adolescents express more pain compared to males and pre-adolescents and adults, respectively.[33] However, evidence regarding this issue is quite contradictory. Many studies showed no significant difference between males and females in pain expression.[8,9,11,12] In addition, some authors reported that orthodontic pain perception is not affected by patient's age.[34] In order to eliminate these possible confounding variables, in the present study random sampling was applied by matching age and gender in studied groups.

Pain is a mental reaction to nervous stimulants whose intensity depends on personal differences, sleeping quality, physiologic conditions, genetics, hormonal differences, and previous painful experience.[6,16] In this study, it is tried to minimize the effects of these factors using a randomized clinical trial method of split-mouth and high volume of samples.

Considering the fact that pain is a subjective issue and shows great interpersonal variability, split-mouth design was chosen for this study. It has been shown that split-mouth design can decrease interpersonal variations.[35,36] Nevertheless, this design may have some problems. Hujoel et al. have reported three potential problems of this design: (1) presence of carry-across effect (i.e. the intervention in one side can affect the other side); (2) difficulty of finding samples with similar conditions on both sides; (3) being more efficient than parallel design only in cases that within-patient correlation coefficient is high.[37−39] In this study, finding patients with intact dentition in mandible was not a problem. In addition, interpersonal differences in pain perception are substantial. However, carry-across effect is a possible problem. To decrease this problem, we designed the present study in a way that two active interventions (menthol and benzocaine) are given to different people (parallel design), but to decrease interpersonal differences in pain perception, one side in each patient was chosen as placebo (split mouth). Afterwards, patches effects are mainly topical. However, solubility in saliva is still possible and cannot be neglected. It is suggested that in future studies, unidirectional patches be administrated. These patches release the drug from only one side.[19]

In present study, patches were chosen as a method of drug delivery. Patches are suitable carriers for drugs in oral cavity since there is extensive smooth, immobile mucosa to retain the patch. Capability of delivering the drug to affected area (topical action), reaching the desired dose in the site, and retaining for a more prolonged time are advantages of patches over some other traditional methods. Patches should be elastic, flexible, and have good tear resistance.[19] These characteristics were considered during patch production in present study. None of the patients in the present study reported adverse reactions related to patches.

The main limitations of this study were difficulty in persuading patients in terms of accurate use of patches and filling out questionnaires in determined times, limited number of articles investigating menthol, especially in dentistry field, and impossibility of direct and precise measurement of pain regarding subjective and personal nature of it. Due to lack of enough studies regarding use of menthol patches in reducing orthodontic pain, it is suggested that more research should be done on the effect of this material on different stages of orthodontic treatment with various concentrations and applying protocols.

In conclusion, menthol and benzocaine patches have been significantly effective in reducing pain resulted from elastomeric separators and both of them could be used as an analgesic agent after placing elastomeric separators. Although benzocaine patch was superior to menthol patch in relieving pain, this difference was not statistically significant.

FUNDING

None.

ETHICAL APPROVAL

This study was approved by Ethics Committee of Hamedan University of Medical Sciences (IR.UMSHA.REC.1395.225) and registered at Iran Registry of Clinical trials with code of (IRCT2016080129155N1).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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