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Original Article

Effect of preoperative systemic capsaicin on tooth sensitivity after in-office bleaching: A pilot study

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ABSTRACT

Background: Tooth bleaching sensitivity (TBS) after bleaching procedures is a common problem. This study was undertaken to determine the effect of preoperative systemic capsaicin on tooth sensitivity (TS) after in-office bleaching procedures.

Materials and Methods: Thirty participants received the treatment in this clinical trial. The subjects were randomly assigned to two groups (n = 15). Placebo and 0.25% capsaicin were administered three times daily for 24 h, with the first dose being administrated 1 h before the bleaching procedure. The subjects underwent two bleaching sessions at a 2-week interval by applying 40% hydrogen peroxide gel on six upper anterior teeth. A visual analog scale (VAS) was used to evaluate TS. Data were analyzed with SPSS 24. Statistical analyses were carried out with the Wilcoxon test and paired t-test. Statistical significance was set at $P \leq 0.05$.

Results: In the capsaicin group, there was a significant increase in TBS between the immediate and 1-h postoperative intervals and a significant decrease between 1- and 24-h postoperative intervals ($P = 0.01$ and $P = 0.000$, respectively). In the placebo group, there was a significant decrease between immediate and 24-h and between 1- and 24-h postoperative intervals ($P = 0.007$, $P = 0.02$). Milder TS was detected in the placebo group 24 h after bleaching ($P < 0.05$).

Conclusion: Under the limitations of this study, preoperative use of systemic capsaicin did not significantly affect TS after the in-office bleaching procedure.

Key Words: Capsaicin, tooth bleaching, tooth sensitivity

INTRODUCTION

Vital tooth bleaching is safely and effectively applied on discolored teeth,[1] The in-office bleaching technique is carried out with the use of 10%–40% hydrogen peroxide,[2] although the maximum hydrogen peroxide concentration which considered to be safe by the Scientific Committee on Consumer Product in Europe is 6%.[3] Tooth bleaching sensitivity (TBS) after bleaching procedures is still a problem. A high incidence rate of TBS is most common within the first 24 hours after in-office bleaching treatment with high concentrations of peroxides.[4] Studies have reported a 30%–87% rate

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of incidence for TBS, which explains why patients discontinue treatment.[1]

Different techniques have been used to decrease bleaching-induced tooth sensitivity (TS). Preoperative administration of 600 mg of ibuprofen decreased TBS only during but not after the procedure.[5] Furthermore, preoperative administration of 400 mg doses of ibuprofen 48 h after bleaching decreased sensitivity during and immediately after the procedure for a maximum of 1 h.[6] Administration of 60 mg of etoricoxib (a COX-2 selective anti-inflammatory agent) decreased TBS.[1] However, the results of a recent systematic review indicated that oral anti-inflammatory drugs have no clinically significant effect on TS due to in-office bleaching.[7] Preoperative application of 5% potassium nitrate and 2% sodium fluoride decreased TS after bleaching.[8] Another study indicated that the application of a desensitizing gel based on 5% potassium nitrate was not effective in decreasing TBS.[9] In addition, the use of 1.23% fluoride gel before an at-home bleaching procedure decreased TS.[10] Administration of a 500-mg dose of ascorbic acid did not prevent and decrease TS after in-office bleaching procedures.[11] The use of nano-hydroxyapatite paste effectively decreased TS.[12] Using dexamethasone to reduce TS after bleaching proved to be ineffective.[13]

An increase in substance P (SP) levels within the pulp in bleached teeth was deemed responsible for neurogenic inflammation and pain.[14] It seems that penetration of peroxide through enamel and dentin and activation of vanilloid receptor 1 (VR1) result in increased pulpal expression of SP and development of TBS.[15] Capsaicin, a component of chili peppers, is believed to be a highly selective agonist for VR1 receptors.[16] Different forms of capsaicin have previously been used to relieve pain.[17,18] Upcoming studies have implicated that capsaicin has great potential to become a first- or second-line treatment option for neuropathic pain, and for many other pain-related states.[19] Therefore, this study investigated the effect of preoperative use of systemic capsaicin on TBS induced by in-office bleaching. The null hypothesis of the current study is that the use of systemic capsaicin had no effect on TBS induced by in-office bleaching.

MATERIALS AND METHODS

The protocol of this clinical trial was approved by the Scientific Review Committee and the Committee for the Protection of Human Subjects of Isfahan University of Medical Sciences under the code #395183, and the clinical trial registration number is IRCT2015122825729N1. All procedures performed in studies involving human participants were by the ethical standards of the Institutional and/or National Research Committee (Name of Ethics Committee: Research chancellery of Isfahan University of Medical Sciences, Approval date: June 06, 2016, Ethics committee reference number: ir.mui.rec. 1395.3.193) and were with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed written consent was obtained from all the subjects. The experimental protocol was based on the CONSORT statement.

This clinical investigation was a randomized, single-blind (subjects were blinded), placebo-controlled, crossover study with an equal chance for the subjects to receive both treatments. A total of 108 subjects were examined to determine whether they met the inclusion criteria or not, and 30 subjects were finally included in the study [Figure 1]. The subjects included in this clinical trial were 18–32 years old and exhibited good oral health. All the subjects had six caries-free maxillary anterior teeth, without any restorations on the labial surfaces. None of the subjects were smokers. The central incisors exhibited C2 shade or darker, as judged by the middle third of the labial surface with the use of a value-oriented Vita shade guide (Vita Classical Shade Guide, Vita Zahnfabrik, Bad Sackingen, Germany). Subjects with a medical history necessitating special considerations, those currently taking anti-inflammatory drugs and pain relievers, those who were pregnant or breastfeeding a child, those with an oral lesion, with calculus or heavy stains, and those with a history of TBS like dentin exposure and recession, and those who recently used desensitizing products were excluded from the study [Table 1].

The primary outcome was the absolute risk of experiencing TBS. A study reported this risk to be approximately 90%.[6] To be able to detect an absolute difference of 25% between Groups 1 and 2, a sample size of a minimum of 30 patients was required with a power of 90% at $\alpha = 5\%$.

The subjects were randomly assigned to one of the two groups: 0.25% capsaicin every 8 h for 24 h or placebo every 8 h for 24 h, followed by a crossover to the other regimen after 2 weeks. Simple randomization

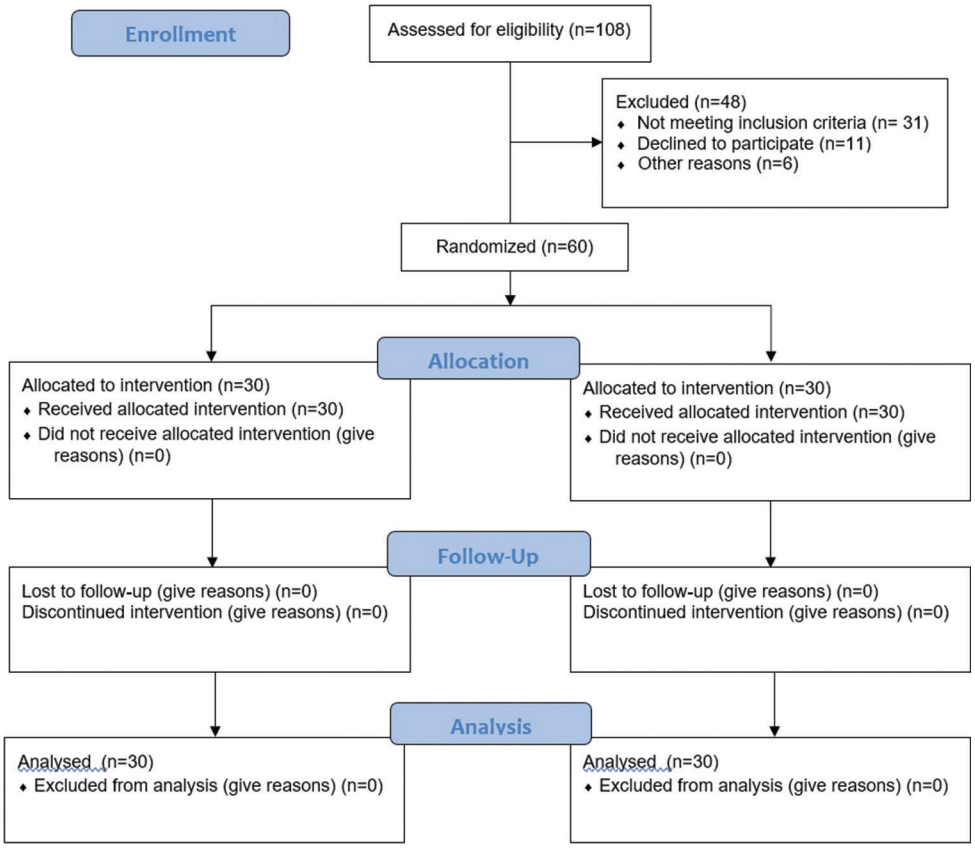

Figure 1: Flow diagram of the clinical trial, including detailed information on the excluded participants.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
At least 18 years old	Active caries and/or
Good oral hygiene	periodontal diseases or
Have six caries-free maxillary	medical problems
anterior teeth	Pregnant or lactating
No restoration on the labial	Oral lesion
surface of the six maxillary	Calculus or heavy stain
anterior teeth	Dentin exposure and
Central incisors were C2 or	recession
darker	Currently, use
No history of smoking, tooth	anti-inflammatory drugs
sensitivity	and pain relievers
Don't use desensitizing products	No schedule availability

was carried out by allocating an even number to the group receiving the drug first and an odd number to the group receiving the placebo first. The subjects in the placebo and capsaicin groups received placebo (starch powder) and 0.25% capsaicin (50 mg powder of capsicum with 0.25% capsaicin) 1 h before treatment, respectively. The subsequent doses of placebo and capsaicin were administered every 8 h after the first dose over 24 h. Both the drug and placebo capsules were prepared by a pharmaceutical company with an identical appearance. The procedure was repeated after 2 weeks before the second treatment session. The subjects were given a phone call to remind them that they had to take their drug doses.

The gingival tissue of the teeth that were supposed to undergo a bleaching procedure was isolated from and protected against the bleaching agent using a light-cured resin dam (OpalDam, Ultradent Products, Inc, USA). A VALO Cordless light-curing unit (C 25668, Ultradent Products, Inc, USA) was used in this study. The in-office bleaching technique was undertaken with the use of 40% hydrogen peroxide (Opalescence Boost PF 40%, Ultradent Products, Inc, USA) in two 20-min sessions 2 weeks apart according to the manufacturer's instructions.

Shade was evaluated before and 16 days after the procedure, using a subjective technique with a numeric value-based Vita shade guide (Vita Classical Shade Guide, Vita Zahnfabrik), which consisted of 16 shade guide tabs arranged from the highest (B1) to the lowest (C4) value, with shade C2 tab being the seventh on the arrangement. Two well-trained and calibrated operators evaluated the middle third of the labial surface of central incisors for shade matching. To calibrate operators, four subjects who were not included in the sample were

used for the training phase of this study. The two operators scheduled these subjects for bleaching with Opalescence Boost PF 40% without administration of placebo or capsaicin and evaluated their teeth against the shade guide before and after bleaching. The two operators exhibited an agreement rate of 85% (kappa coefficient) before the study. The shade comparison before and after the procedure was displayed by the difference between the baseline and 16-day interval shades (ΔSGU). The patients recorded their TBS during the two bleaching sessions using VAS, consisting of a 100-mm horizontal line, with one end indicating "no pain" and the opposite end indicating "worst pain." The subjects recorded their TBS 1 h before treatment, immediately after treatment, and at 1- and 24-h intervals after treatment.

Data were analyzed with SPSS 24 (SPSS Inc. Chicago, IL, USA). The absolute risk, means, and standard deviations were calculated in each group. TBS data did not appear to be normally distributed. Therefore, statistical analyses of VAS to compare the two groups at four different time intervals were carried out with the Wilcoxon test and paired *t*-test ($\alpha = 0.05$). A paired *t*-test was used to make comparisons between the time intervals within each group and between groups at each time interval. Color changes were used for the assessment of the efficacy of the bleaching procedure in association with the preoperative application of capsaicin. The Δ SGU values were analyzed with Student's *t*-test in both groups. Statistical significance was set at $P \leq 0.05$.

RESULTS

Thirty patients, including 18 females and 12 males, were evaluated in this study. Figure 1 depicts the subjects' flow diagram in different phases of the study. About the absolute risk, there was no significant difference between the groups [Table 2; $P = 0.23$]. The means, minimums, and maximums of VAS scores are presented in Table 3. The mean TS intensity reported by the subjects after administration of placebo and capsaicin is presented in Figure 2.

Concerning TBS intensity, there was a significant difference between the groups at 1- and 24-h postoperative intervals ($P = 0.007$ and $P = 0.05$, respectively). In the capsaicin group, there was a significant decrease in TBS between 1- and 24-h postoperative intervals and a significant increase between the immediate and 1-h postoperative intervals ($P = 0.000$ and $P = 0.01$, respectively). In the placebo group, there was a significant decrease between 1- and 24-h postoperative and immediate and 24-h postoperative intervals ($P = 0.02$, $P = 0.007$).

Both groups exhibited significant whitening ($P < 0.002$). The placebo and capsaicin groups exhibited whitening of around 5.1 and 4.2 shade guide units, respectively.

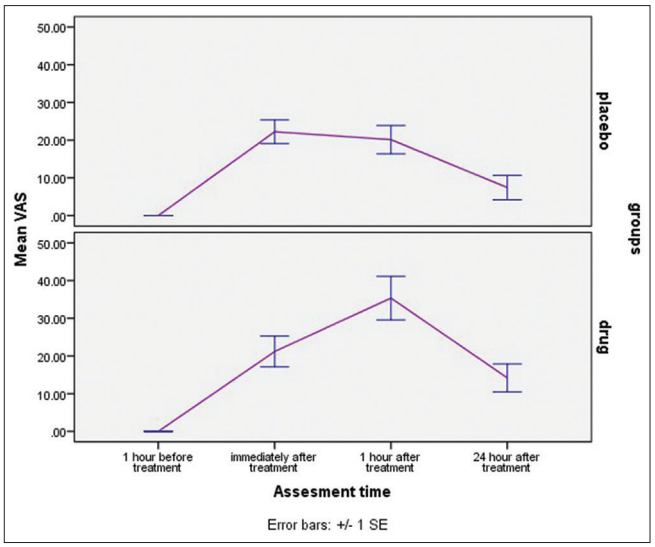

Figure 2: The effect of capsaicin on VAS. VAS: Visual analog scale.

Table 2: Absolute and relative risk of tooth sensitivity in groups

Treatment	Number of patients with TS		Absolute risk (95% CI)	Relative risk (95% CI)
	Yes	No		
Placebo	30	0	100 (0.0–100.0)	1.11 (0.98–1.25)
Capsaicin	27	3	90 (5.0–95.0)	

*Fisher's test (P=0.23). CI: Confidence interval; TS: Tooth sensitivity

Table 3: The means, minimums, and maximums of VAS scores

Assessment time	Groups	*n*	Mean (SD)	Minimum	Maximum
Immediately after treatment	Placebo	30	22.2 (17.1)	0	60.0
	Capsaicin	30	21.1 (22.3)	0	93.5
	Total	60	21.7 (19.7)	0	93.5
1 h after treatment	Placebo	30	20.1 (20.5)	0	72.0
	Capsaicin	30	35.3 (31.6)	0	87.0
	Total	60	27.7 (27.5)	0	87.0
24 h after treatment	Placebo	30	7.4 (17.7)	0	75.0
	Capsaicin	30	14.1 (20.1)	0	55.0
	Total	60	10.8 (19.1)	0	75.0

SD: Standard deviation

DISCUSSION

In the present study, the null hypothesis was rejected as the severity of TS in the placebo group was lower than that in the capsaicin group at 1- and 24-h postoperative intervals and the difference was significant (P = 0.007 and P = 0.05, respectively). The results of this study might help adopt strategies to deplete SP by capsaicin. Capsaicin can deplete SP in sensory nerves and promote the release of SP.[16] An increase in SP levels increases inflammation and pain.[20] Higher levels of pain and sensitivity in the capsaicin group might be explained by an increase in the release of SP. An adequate dose of capsaicin initially results in increased release of SP and then depletion of capsaicin-sensitive sensory neurons of SP. Neurons are desensitized and the nerve transmission is blocked until the reproduction of SP. It seems that dental pulp neurons were desensitized since capsaicin receptors (VR1) were found in the pulp. It is assumed that subjects did not experience TBS during this period of desensitization.

A study showed that capsaicin mouth rinse can decrease the severity of pain associated with burning mouth syndrome (BMS).[21] However, most studies have used topical capsaicin to reduce pain.[17,18,21] In this study, the systemic form was administrated due to the slow delivery of capsaicin through the skin into the systemic circulation and low serum concentration following topical use.[17] Topical application of capsaicin is more common, but it usually induces irritation;[17] to prevent gingival irritation which seems to happen following topical use of capsaicin, the systemic administration of prepared capsules containing capsaicin powder was used. Previous studies have shown that 0.25% systemic oral capsaicin is effective in BMS.[18,22] One study showed no side effects,[22] but another study showed that 32% of the patients taking it exhibited gastrointestinal pain. It should be pointed out that short-term application of systemic capsaicin is safe.[18] It has been reported that the oral lethal dose of capsaicin in humans is 0.5–5 g/kg[23] and metabolized in the liver.[17] The received capsaicin dose per day in this study was even much lower than the mean intake of capsaicin from industrially prepared food products.

TBS after tooth bleaching procedures may result from pulpal inflammation due to the penetration of peroxide through the enamel and dentin.[1,6,23] Histological evaluations of the dental pulp have shown that bleaching with 10% carbamide peroxide led to a mild inflammatory response at 4- and 14-day postoperative intervals.[5]

Given the relationship between the inflamed pulp and TBS, several studies have suggested the preoperative administration of anti-inflammatory agents.[1,5,6] However, they proved ineffective in preventing TS after bleaching procedures. This might be explained by the release of bradykinin and SP, which are not blocked by ibuprofen and etoricoxib. Therefore, capsaicin was used in this study to block SP and decrease the severity of TBS.

The results of this study showed a significant difference in TS of the subjects in the capsaicin group at 1- and 24-h postoperative intervals. Although TS decreased significantly, at 24-h postoperative interval, the sensitivity in the capsaicin group was significantly higher than that in the placebo group. Repeated application results in desensitization, inhibiting the release of SP.[17,24] We believe that the severity of sensitivity in the capsaicin group would have been less than that in the placebo group if follow-ups had continued. It is suggested that the same study protocol be used over a long period to investigate this hypothesis.

Opalescence Boost PF 40% was used in this study, although it is much higher than what is considered to be safe in Europe but not much higher than those used in the USA.[3] There was a 2-week interval between the two bleaching sessions because the inflammatory process induced by bleaching usually continues for 2 weeks.[14]

The efficacy of drugs is affected by the dose and the time interval between administration and the procedure. After the application of a patch with a high concentration of capsaicin, systemic capsaicin levels decreased very rapidly with a mean half-life of 1.64 h.[16] When capsaicin is administrated orally, it is passively absorbed from the stomach and intestine. Animal studies indicate wide-spread distribution; a range of 1%–24% of the administered volume can be detected in the blood, liver, and kidneys of rats up to 24 h after its consumption.[25] A human study found consumption of 26.6 mg of capsaicin, which is equal to eating two and a half jalapeño peppers, causes a maximum plasma concentration of approximately 2.47 ng/mL and a half-life of about 30 min.[26] In our pilot study, the inefficacy of the drug might be explained by a lack of precise information to

determine the proper dose and interval before administration of capsaicin, additional research is required in this regard.

Adverse effects of capsaicin are itch, pain, burning sensation, and irritation due to topical use.[17] Since it is administrated systemic, patients may exhibit gastrointestinal pain, but the short-term application of systemic capsaicin is safe,[18] which is administrated over 24 h in this study. As mentioned, TBS is most common during the first 24-h period following treatment; thus, to reduce that, it does not need a long-term administration of capsaicin. It is suggested that systemic capsaicin be used in the same protocol study over a long follow-up period to evaluate long-term side effects.

Another explanation is the fact that men and women react differently to the pain experience, with controversies over personal differences in the subjective rating of capsaicin pain between males and females. Studies have shown that menstrual cycles and the use of oral contraceptives result in different pain ratings in women.[27] In this study, although each subject was compared with himself/herself, menstrual cycle and use of oral contraceptives before and between the bleaching sessions were not evaluated.

It has been reported that enamel craze lines might increase TS.[28] Another limitation of this study is the teeth were not screened for enamel craze lines. Since no correlation has been reported between tooth thickness and bleaching-induced TS,[29] we did not determine the thickness of the bleached teeth.

It has been shown that potassium nitrate and sodium fluoride are effective in decreasing TBS.[30] The inefficacy of capsaicin might be explained by the presence of potassium nitrate and fluoride in 40% Opalescence Boost PF according to the data provided by the manufacturer. Furthermore, this might be a reason for decreased sensitivity in the placebo group. Another limitation of this study was the fact that the subjects did not use a single toothpaste with the same fluoride and potassium nitrate concentrations.

Concerning the outcomes of bleaching, this was not the primary objective and was used as an indicator that subjects had bleached their teeth; the results of the present study showed similar and significant tooth shade improvement in the two groups, compared to baseline values. It is difficult to compare the shade changes after in-office bleaching with those reported in the literature, which is due to the use of different methods of measurement (shade guides and spectrophotometry) and also differences in measurement units (CIELAB system and shade guide units). However, studies using 35% hydrogen peroxide reported their results in shade guide units, with an overall shade change of 5–8 shade guide units after two bleaching sessions,[6,8] consistent with the results of the present study.

Finally, it should be pointed out that the subjects are mainly composed of young individuals, which limits the ability to generalize the findings of this study to the general population consisting of older adults.

This study has some limitations, including a concise follow-up period, lack of previously released information to determine the proper dose of capsaicin administration, and the probability of confounders, as mentioned above. The authors suggest that systemic capsaicin be used in the same protocol study over a long follow-up period with a larger population to evaluate long-term side effects.

CONCLUSION

Under the limitations of the present study, it was concluded that the preoperative systemic administration of 0.25% capsaicin for 24 h, starting 1 h before treatment, did not significantly affect the intensity of TS induced by in-office bleaching.

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Conflicts of interest
The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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