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The antiplaque and bleeding control effects of a cetylpyridinium chloride and tranexamic acid mouth rinse in patients with gingivitis

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ABSTRACT

Purpose: This study aimed to evaluate the effects of a cetylpyridinium chloride (CPC) and tranexamic acid (TXA) mouth rinse on patients with gingivitis.

Methods: This randomized, placebo-controlled, double-blind, parallel-group, clinical trial included 45 healthy adults with gingivitis, who were randomized into 2 groups. The experimental group used a 0.05% CPC and 0.05% TXA mouth rinse, and the control group used a placebo mouth rinse. The following clinical indices were assessed at baseline, at 3 weeks, and at 6 weeks: the Turesky-Quigley-Hein plaque index (QHI), the Löe-Silness gingival index (GI), and bleeding on marginal probing (BOMP). The subjects used the mouth rinse during the experimental period for 20 seconds, 4–5 times daily (10 mL each time).

Results: There were no significant differences in the clinical indices between the groups at baseline. In the experimental group (CPC+TXA), a statistically significant improvement was evident in the QHI, GI, and BOMP at 3 and 6 weeks. These results were similar to those observed in the control group at 3 and 6 weeks, although the change in BOMP was not statistically significant in that group. At 6 weeks, the experimental group had a significantly lower mean score for the QHI than the control group.

Conclusions: This study demonstrated that a CPC and TXA mouth rinse exhibited significant antiplaque and anti-gingivitis efficacy, and had a positive effect on bleeding control when used daily for 6 weeks.

Keywords: Cetylpyridinium; Dental plaque index; Prevention mouthrinse; Tranexamic acid

INTRODUCTION

Dental plaque causes inflammation and periodontal disease [1,2]. Bacteria locally attach to the intra-oral regions and proliferate, thereby inducing chronic inflammatory and autoimmune responses. The treatment of periodontal disease includes non-surgical and surgical treatments, such as scaling, root planing, flap operations, and guided tissue regeneration with new attachments. Treatment is followed up by regular daily home care, in which the patient maintains oral hygiene [3].

Author Contributions
Conceptualization: Jae-Mok Lee, Yong-Gun Kim; Data curation: Youngkyun Lee, Yong-Gun Kim; Formal analysis: Ji-Eun Lee, Heung-Sik Um, Yong-Gun Kim; Funding acquisition: Jae-Mok Lee, Yong-Gun Kim; Investigation: Ji-Eun Lee, Yong-Gun Kim; Methodology: Jin-Woo Park, Jo-Young Suh, Heung-Sik Um, Yong-Gun Kim; Project administration: Jae-Mok Lee, Yong-Gun Kim; Resources: Ji-Eun Lee, Jae-Mok Lee, Youngkyun Lee, Jin-Woo Park, Jo-Young Suh; Software: Yong-Gun Kim; Supervision: Yong-Gun Kim; Validation: Heung-Sik Um, Yong-Gun Kim; Visualization: Ji-Eun Lee, Yong-Gun Kim; Writing - original draft: Ji-Eun Lee; Writing - review & editing: Jae-Mok Lee, Yong-Gun Kim.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Good oral hygiene is maintained at home with adequate tooth brushing. However, perfect oral hygiene via mechanical dental plaque control, such as tooth brushing, should not be expected of the patient. Nonetheless, the long-term success of periodontal treatment is determined by the maintenance of dental plaque control. Therefore, daily oral hygiene control may be improved by the combination of proper tooth brushing and the use of adjunctive antiplaque agents in a mouthwash [4].

Mouthwash efficacy is determined by its ability to prevent plaque accumulation and to resolve inflammation. Additional emphasis is also placed on its capacity to penetrate intraoral tissue, and to maintain a lasting, effective concentration within the oral cavity. As such, the following antiplaque agents for mouthwash are currently recognized within the literature: alexidine (ALX), delmopinol, essential oils (EOs), hexetidine (HEX), stannous fluoride, chlorhexidine (CHX), and cetylpyridinium chloride (CPC) [5]. Serrano et al. [6] reported that tooth brushing with the adjunctive use of the biguanide-class antimicrobial agent, ALX, managed to prevent the accumulation of dental plaque and the incidence of gingival inflammation after a 6-month treatment regimen. Additionally, the use of a third-generation antiplaque agent, delmopinol, likewise reduced dental plaque levels and alleviated gingivitis. In contrast, EOs collapse the cell walls and precipitate cell proteins at high concentrations, and deactivate essential enzymes at low concentrations. HEX, which is a derivative of pyrimidine, is a broad-spectrum but short-lasting antibiotic, while stannous fluoride, which is a commercially available fluoride product, has effective antimicrobial activity and further reduces the incidence of dental caries. Nonetheless, CHX is currently the most effective and long-lasting antiplaque agent available; it acts on both Gram-negative and Gram-positive bacteria, in addition to facultative anaerobic bacteria. However, side effects have been reported, including the following: discoloration of the teeth and tongue, parageusia, irritation of the mucous membrane, and hypersensitivity reactions with long-term use [5,7]. CPC, which is a cationic quaternary ammonium compound, has been suggested as an alternative to CHX. CPC is an effective product for controlling dental plaque accumulation; it eliminates the bacteria that cause periodontal diseases, and therefore prevents the incidence of gingivitis and halitosis. Nonetheless, it is somewhat less effective than CHX for preventing dental plaque accumulation, but this is offset by the presence of substantially fewer side effects, such as the discoloration of teeth, than occur with CHX mouth rinse. The antiplaque effect of CPC is attributable to the cationic component of CPC, which easily attaches to the negatively charged proteins of the intraoral tissue [6,8,9].

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine. It induces antifibrinolytic effects by reversibly inhibiting the lysine binding sites of plasminogen molecules. TXA has a binding affinity that is 6–10 times higher than that of ε-aminocaproic acid for the plasminogen/plasmin binding site [10]. When administered systemically, TXA is not found in the saliva; further, the plasma TXA concentration obtained after use of a 5% weight/volume aqueous solution in a mouth rinse was clinically insignificant, with levels <2 mg/L [11]. Nevertheless, in a study investigating the postoperative oral hygiene management of patients who underwent intraoral operations and who were taking anticoagulants for cardiovascular diseases, the effectiveness of TXA was assessed with the international normalized ratio, which showed a decrease from 3.0–4.5 to 1.5–2.5, compared to the control group [12-14]. The percentage of patients with the complication of postoperative hemorrhage in the TXA group was 0%–6.7%, compared to 13.3%–40.0% in the control group. Moreover, it was indicated that the use of 5% TXA mouthwash, 4 times daily for 2 days, may prevent fibrinolysis. There have been many studies detailing the preventative hemostatic action of TXA on the incidence of postoperative bleeding following intraoral surgical treatments.

Nonetheless, little is known about the effects of TXA mouthwash on periodontal disease-associated inflammatory bleeding.

The purpose of this study was to evaluate the effects of a CPC and TXA mouth rinse on the clinical prevention of dental plaque accumulation, gingivitis, and gingival bleeding over a 6-week period in patients with gingivitis.

MATERIALS AND METHODS

Patient selection

Forty-five patients (24 male patients and 21 female patients) with gingivitis or mild periodontitis visited the Department of Periodontology, Kyungpook National University Dental Hospital, and voluntarily agreed to participate in the clinical study. The mean age of the patients was 28.7 years.

Patients who fulfilled the following inclusion criteria were selected: 1) aged between 18 and 70 years; 2) a minimum of 20 natural teeth (excluding the third molar); 3) good general health; 4) no history of allergies or hypersensitivity to CPC and TXA; 5) non-smokers; 6) a mean Turesky-Quigley-Hein plaque index (QHI) of at least 1.5; 7) a mean Löe-Silness gingival index (GI) of at least 1.0; and 8) the provision of informed, written consent. Patients were excluded from the trial based on the following criteria: 1) failure to meet the inclusion criteria; 2) severe periodontitis or caries; 3) use of mouthwash of any kind on a daily basis for oral hygiene control; 4) use of removable partial dentures; 5) evidence of an observable lesion in their oral cavity (excluding aphthous stomatitis); 6) use of orthodontic appliances (except lingual retention wire); 7) being pregnant or lactating; and 8) being in poor general health or having a deficient immune response.

The protocol was reviewed and approved by the Institutional Review Board (IRB) of the dental hospital of Kyungpook National University (IRB File No. 2015-08-020-006). The study was conducted in accordance with the tenets of the Helsinki Declaration.

Materials

The experimental group used GUM Dental Rinse S (GUM, Sunstar Inc., Osaka, Japan), while the control group used a placebo mouthwash. GUM Dental Rinse S is a mouth rinse containing 0.05% CPC and 0.05% TXA. The placebo mouthwash consisted only of the additives, containing neither CPC nor TXA. A disclosing solution (GUM Red Cote, Sunstar Butler, Chicago, IL, USA) was used to evaluate the QHI. During the experimental period, the subjects used a smooth toothbrush (Butler #233, Sunstar Butler) and a sodium lauryl sulfate-free toothpaste. The use of oral hygiene products other than toothpicks was strictly prohibited.

Clinical parameters

The QHI, GI, and the bleeding on marginal probing (BOMP) index were measured as clinical parameters [15]. Dental plaque accumulation was evaluated via QHI. QHI uses a disclosing agent to measure and evaluate the 6 regions (lingual, distolingual, mesiolingual, buccal, distobuccal, and mesiobuccal) of each Ramfjord tooth. The scoring system was as follows:

> 0=no dental plaque;
> 1=the presence of a discontinuous line of dental plaque at the gingival margin;
> 2=a continuous line of dental plaque at the gingival margin that does not extend further than 1 mm from the margin;

3=dental plaque coverage that is greater than 1 mm, but does not extend further than one-third of the tooth;

4=dental plaque that covers more than one-third but not more than two-thirds of the tooth surface;

5=dental plaque coverage over more than two-thirds of the tooth surface.

Gingivitis was evaluated using the GI, which measures the severity of inflammation in the marginal gingiva. The degree of inflammation was scored from 0 to 3:

0=normal gingiva;

1=mild inflammation: slight change in the color and slight edema; no bleeding on probing;

2=moderate inflammation: redness, edema, and glazing; bleeding on probing;

3=severe inflammation: marked redness and edema; ulceration; tendency for spontaneous bleeding.

The degree of gingival bleeding was evaluated by BOMP, which assesses the presence or absence of bleeding within 30 seconds following probing of the marginal gingiva with a periodontal probe. The bleeding was scored from 0 to 2:

0=no bleeding;

1=pin prick;

2=excess.

Experimental design

Prior to the clinical trial, the patients received instructions on oral hygiene and tooth brushing. The periodontal clinical parameters (QHI, GI, and BOMP) were measured at baseline, at 3 weeks, and at 6 weeks. During the experimental period, the subjects used 10 mL of the mouthwash 4–5 times daily (after meals and before bedtime) for 20 seconds each time. The experimental protocol is described in Table 1 and Figure 1.

Table 1. Overview of the experimental protocol

Parameters	Visit 0 (−2 wk)	Visit 1 (baseline)	Visit 2 (3 wk)	Visit 3 (6 wk)
Informed consent	○	-	-	-
Subject selection	○	-	-	-
Oral hygiene instruction	○	-	-	-
QHI	○	○	○	○
GI	○	○	○	○
BOMP	-	○	○	○

QHI: Turesky-Quigley-Hein plaque index, GI: Löe-Silness gingival index, BOMP: bleeding on marginal probing.
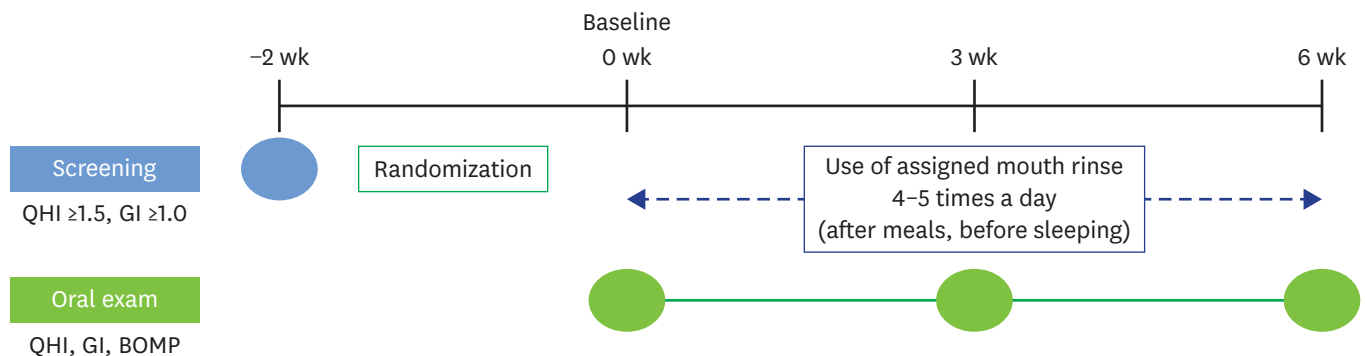

Figure 1. Overview of the experimental protocol.
QHI: Turesky-Quigley-Hein plaque index, GI: Löe-Silness gingival index, BOMP: bleeding on marginal probing.

Statistical analysis

Statistical analysis were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). For the analysis of the patients' age, sex, the Mann-Whitney U test and the χ^2 test were conducted for the experimental and placebo control groups. The Friedman test was conducted to determine the differences in the clinical parameters (QHI, GI, and BOMP) with respect to time. The differences between the 2 groups at each point of time (baseline, 3 weeks, and 6 weeks) were evaluated using the Mann-Whitney U test. Statistical significance was defined as a P value <0.05.

RESULTS

The experimental group included 23 patients (12 male patients and 11 female patients), and the control group included 22 patients (12 male patients and 10 female patients) (P=1.000). The mean age of the patients was 28.7 years, with no significant statistical difference evident between the experimental group (28.3 years) and the control group (29.1 years) (P=0.846). As indicated in Table 2, all patients were non-smokers. By the end of the study, there were no reports of patient discomfort or cases of abnormal signs (discoloration of the teeth and tongue, incidence of parageusia, mucosal irritation, or hypersensitivity).

QHI

The mean QHI value at baseline was 2.17±0.26 for the experimental group, and 2.12±0.25 for the placebo control group (Table 3, Figure 2). There was a statistically significant difference for both groups between the QHI values at baseline and at 3 weeks (P<0.050). Between 3 and 6 weeks, the mean QHI value decreased in both groups, but this result was not statistically

Table 2. Background information of the patients

Parameters	Total	CPC+TXA group	Placebo group	Intergroup
No. of patients	45	23	22	χ^2 test
No. of males	24 (53.3)	12 (52.2)	12 (54.5)	P=1.000
No. of females	21 (46.7)	11 (47.8)	10 (45.5)	
Mean age (yr)	28.7	28.3	29.1	Mann-Whitney U test
Standard deviation	2.9	2.6	3.2	P=0.846
No. of smokers	0 (0)	0 (0)	0 (0)	-
No. of non-smokers	45 (100)	23 (100)	22 (100)	

Values are presented as number (%).
CPC: cetylpyridinium chloride, TXA: tranexamic acid.

Table 3. Mean values of the clinical parameters

Parameters	CPC+TXA group (n=23)	Placebo group (n=22)	P value (between groups)
QHI			
Baseline	2.17±0.26	2.12±0.25	0.488
3 wk	1.75±0.27[a]	1.89±0.27[a]	0.111
6 wk	1.63±0.21[a]	1.80±0.25[a]	0.021
GI			
Baseline	1.18±0.24	1.26±0.33	0.426
3 wk	0.74±0.24[a]	0.79±0.24[a]	0.363
6 wk	0.69±0.23[a]	0.79±0.26[a]	0.162
BOMP			
Baseline	0.71±0.34	0.69±0.26	0.946
3 wk	0.50±0.22[a]	0.53±0.27	0.856
6 wk	0.50±0.27[a]	0.60±0.27	0.233

Values are presented as mean±standard deviation. Statistical analyses: Friedman test for intergroup analysis, Mann-Whitney U test for intergroup analysis.
CPC: cetylpyridinium chloride, TXA: tranexamic acid, QHI: Turesky-Quigley-Hein plaque index, GI: Löe-Silness gingival index, BOMP: bleeding on marginal probing.
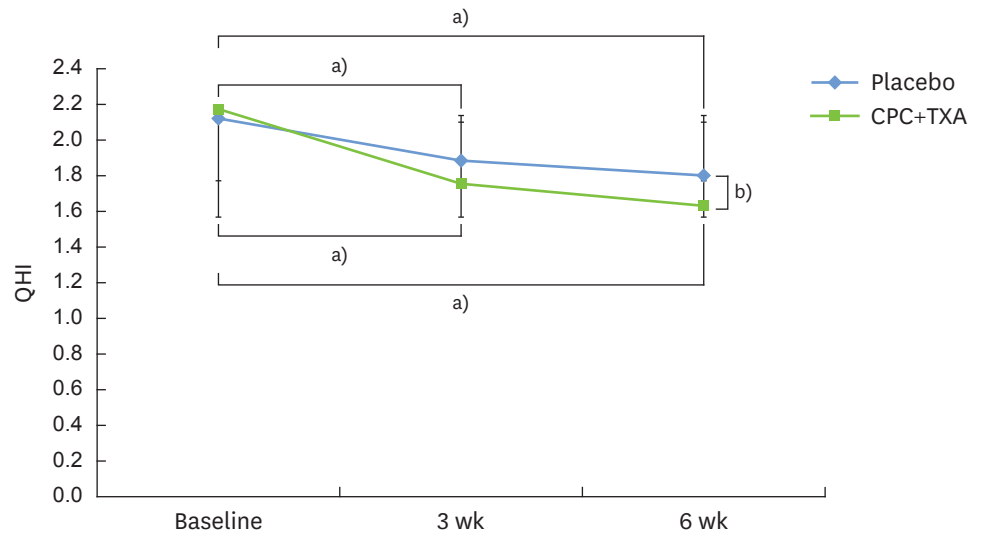[a]Statistically significant difference compared to baseline.

Figure 2. The QHI. Statistically significant differences were evident after 3 weeks of treatment for both groups (experimental group: CPC and TXA, and placebo control group). At 6 weeks, a significant difference was observed in the intergroup analysis. There was a statistically significant difference in the values after 6 weeks of treatment for both groups. Bars represent mean±standard deviation.
QHI: Turesky-Quigley-Hein plaque index, CPC: cetylpyridinium chloride, TXA: tranexamic acid.
[a]Statistically significant intragroup difference compared to the baseline, according to the Friedman test; [b]Statistically significant intergroup difference between the 2 groups at 6 weeks, according to the Mann-Whitney *U* test.
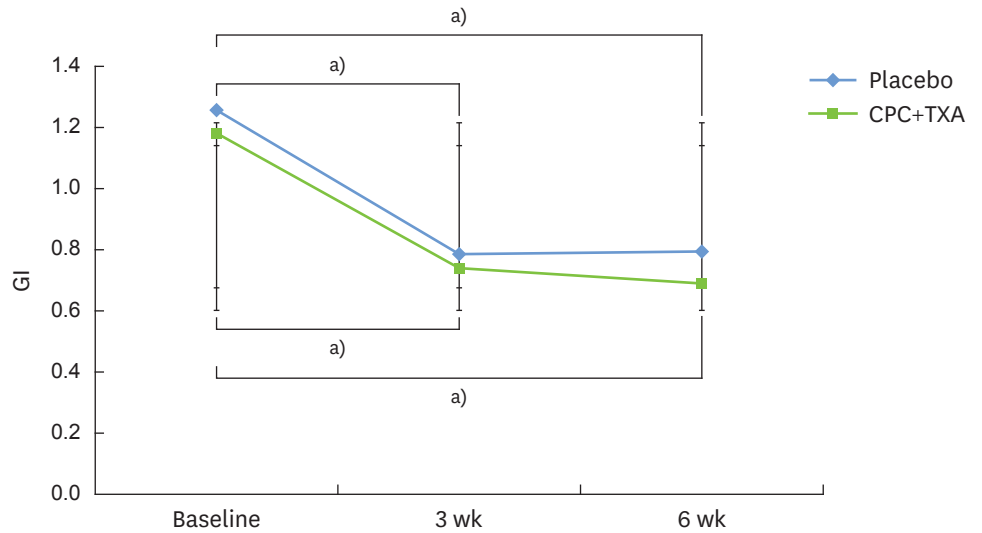

Figure 3. The GI. A statistically significant difference was evident after 3 weeks of using the CPC and TXA mouthwash. Statistically significant differences were found between the values at baseline and those at 6 weeks for both groups. Bars represent mean±standard deviation.
GI: Löe-Silness gingival index, CPC: cetylpyridinium chloride, TXA: tranexamic acid.
[a]Statistically significant intragroup difference compared to baseline, according to the Friedman test.

significant. The mean QHI value significantly decreased after 6 weeks of treatment in both groups ($P<0.050$). Additionally, at 6 weeks, the mean QHI value was 1.63 in the experimental group and 1.80 in the control group. The experimental group and the control group showed statistically significant differences between the mean QHI values at 6 weeks ($P<0.050$).
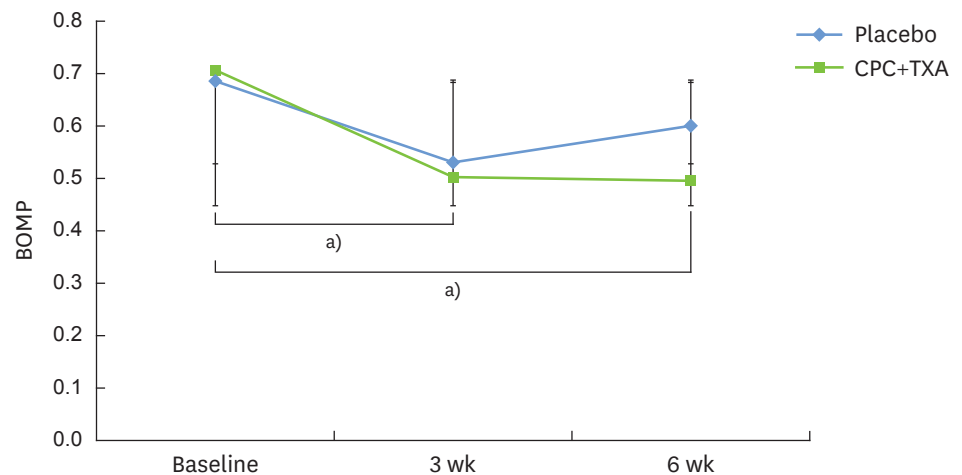
Figure 4. The incidence of gingival BOMP. In the CPC and TXA group, statistically significant differences were observed at 3 weeks and at 6 weeks.
CPC: cetylpyridinium chloride, TXA: tranexamic acid, BOMP: bleeding on marginal probing.
a)Statistically significant intragroup difference compared to baseline, according to the Friedman test.

GI

The mean GI at baseline was 1.18±0.24 in the experimental group, and 1.26±0.33 in the placebo control group (Table 3, Figure 3). Both groups showed statistically significant differences between the values at baseline and at 3 weeks ($P<0.050$). Additionally, a statistically significant reduction was also observed in both groups after 6 weeks of treatment ($P<0.050$). Between 3 and 6 weeks, the GI values of the control group remained unchanged.

BOMP

The mean BOMP score at baseline was 0.71±0.34 in the experimental group, and 0.69±0.26 in the placebo group (Table 3, Figure 4). There were statistically significant differences between the mean BOMP score at baseline and at 3 weeks in the experimental group ($P<0.050$). However, in the placebo control group, there was no statistically significant difference after 3 weeks of treatment. Additionally, there was a statistically significant reduction in the mean BOMP score from the 3-week follow-up (second visit) to the 6-week follow-up (third visit) in the experimental group ($P<0.050$). After 6 weeks, the mean BOMP score for the placebo group was slightly higher than at 3 weeks, but not to a significant extent.

DISCUSSION

The present study demonstrated that a CPC and TXA mouth rinse reduced supragingival dental plaque levels, and alleviated the signs and symptoms of gingival bleeding. This is in accord with several studies; for instance, Shim et al. [16] also showed that similar results could be achieved with a mouth rinse of CPC, triclosan, and dipotassium glycyrrhizinate. Further, White [17] reported that there was a 15.4% reduction in the severity of gingival inflammation, a 33.3% reduction in gingival bleeding, and a 15.8% reduction in dental plaque levels following the use of a high-bioavailability CPC mouth rinse over a 6-month period, in a clinical trial on gingivitis and dental plaque.

The QHI showed statistically significant improvements ($P<0.050$) at 3 and 6 weeks in both groups. Moreover, there was a statistically significant difference between the experimental group

and the placebo control group at 6 weeks. The significant decrease in the mean value of each clinical parameter after 6 weeks of treatment for both the control and experimental groups may have been attributable to the initial provision of extensive oral hygiene education to the patients. However, the significant difference in QHI values between the experimental and control groups at 6 weeks could also be explained by the antiplaque effects of CPC in the mouthwash. Kozak et al. [18] showed that a 0.07% CPC mouth rinse with high bioavailability had antiplaque benefits when used as an adjunctive treatment; dental plaque coverage on teeth significantly decreased, by 42% in comparison to the reductions obtained by tooth brushing alone.

A significant reduction in the severity of marginal gingival inflammation was evident in both groups at 3 and 6 weeks. This significant decrease in the GI during the initial 3 weeks of treatment could also have been explained by the effects of patient education on oral hygiene. Nonetheless, the downward trend in GI values evident in the experimental group may have been attributable to the anti-gingivitis effects of CPC, as there were no changes observed in the mean GI value for the control group from 3 weeks onwards. This observation is similar to that of Gunsolley [19] who reported that the use of CPC mouth rinse decreased the mean GI by 13.4%. In a 6-month clinical study, patients who used 0.075% and 0.10% CPC mouth rinses showed a significantly lower incidence of gingivitis, and had reduced dental plaque accumulation and less severe gingival bleeding by the end of the study period, in comparison to those who used the placebo [20].

BOMP, which is a measure of inflammatory bleeding [21], decreased significantly for the experimental group between the second and third follow-up of the treatment. In comparison, the control group showed a decrease in the mean BOMP value after 3 weeks of treatment, and a slight increase between 3 and 6 weeks. Although these results were not statistically significant, they are potentially attributable to the effects of TXA. Several studies have reported that the administration of TXA had hemostatic effects in the oral cavity during surgical treatment. For example, Carter et al. [22] observed that this was evident in patients taking warfarin undergoing tooth extraction. Additionally, Dunn and Goa [10] reported that TXA mouthwash showed anti-fibrinolytic efficacy in a randomized, double-blind, placebo-controlled study.

The present study is valuable as a clinical study of the effects of a mouth wash containing a combination of CPC and TXA on periodontal disease. The use of mouthwash showed statistically significant results for the control of dental plaque levels and the alleviation of gingival bleeding, with implications for the prevention of gingivitis. Therefore, this study may provide meaningful evidence for further research and may have further clinical applications.

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