Effectiveness of perioperative oral hygiene management using a cetylpyridinium chloride-, dipotassium glycyrrhizinate-, and tranexamic acid-based mouthwash: a randomized controlled clinical trial

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Research Article

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**Abstract**

**Background:** The mouth is a breeding ground for bacteria, and the presence of foreign substances, such as stitches, splints, or skin flaps increases the risk of infection, potentially delaying healing or causing wound dehiscence. Perioperative oral management is thus essential.

Maxillomandibular fixation requires the jawbones to remain static. Mechanical cleaning is also carried out by brushing or with a water flosser to maintain the oral cavity in a hygienic state, but this cannot be considered sufficient.

Mouthwashes are used as a substitute for mechanical cleaning or in a supplementary role after such cleaning. In this study, the effectiveness of HABITPRO mouthwash, which contains cetylpyridinium chloride, dipotassium glycyrrhizinate, and tranexamic acid, was investigated in the specific environment created by maxillomandibular fixation.

**Patients and Methods:** A total of 55 patients who had undergone maxillomandibular fixation were randomly allocated to either a HABITPRO group \( n = 29 \) or a placebo group \( n = 26 \). To investigate their oral hygiene status, their plaque control record (PCR) was reviewed, and the caries-related bacterial counts, pH, acid buffering capacity, white blood cell count, and ammonia in saliva were measured.

**Results:** After the mouthwash had been used for approximately 2–3 weeks, the ammonia level in the HABITPRO group saliva decreased significantly compared with that of the placebo group. The PCR index also increased significantly in the placebo group compared with baseline, whereas it remained almost steady in the HABITPRO group.

**Conclusions:** Even with maxillomandibular fixation, continued gargling with this mouthwash may help maintain a better intraoral environment.

**Introduction**

It has long been known that the oral cavity is a breeding ground for bacteria, because it is not only maintained at a constant temperature, but it is also a moist environment (Aas et al., 2005). The intraoral microbiota is known to change in accordance with the intraoral environment (Akiyama et al., 2010; Sano et al., 2012; Takeshita et al., 2015). As is well known, this means that the environment in the mouth, which anatomically is the entrance to both the digestive tract and the respiratory system, has a range of systemic effects. In addition to the diseases of aspiration pneumonia and diabetes mellitus, its contribution to frailty has also come under scrutiny in recent years (Yoneyama et al., 1999; Lu et al., 2004; Tanaka et al., 2018; Xue et al., 2008).

Under normal circumstances when homeostasis is maintained, individuals are able to coexist with the commensal resident intraoral biota by means of their own immunity and natural purification. However, diminished immunity in the periprocedural period (whether the procedure involves surgery, radiotherapy,
chemotherapy, or another treatment) or due to age means that homeostasis can no longer be maintained, and a range of problems can occur, including wound infection, stomatitis and resulting secondary infection, caries, and periodontitis. Stomatitis is a particular issue during radiotherapy and chemotherapy, and since it causes bleeding and pain, mechanical cleaning becomes difficult (Saadeh et al., 2005). In addition, if food consumption by mouth decreases as a result of mucosal inflammation, nutritional status worsens, and the healing of this mucosal inflammation is delayed in a vicious circle.

The special conditions caused by surgery are also known to affect the oral environment in various ways. For example, patients with a mandibular fracture and those who have undergone corrective surgery may undergo maxillomandibular fixation to encourage bony healing, but this means that they are unable to open their mouths and cannot eat by mouth for a certain period. During this fixation period, physical oral cleaning is inadequate, and the oral environment deteriorates. Brushing and water flossing are used for mechanical cleaning, but this cannot be considered sufficient. Under these conditions, chemical cleaning by gargling with mouthwash has long been used as a supplementary cleaning method. The effectiveness of such chemical cleaning depends on the types and concentrations of the active ingredients.

The objective of this study was to investigate the effect on the intraoral environment of the continued use of a mouthwash containing cetylpyridinium chloride (CPC), dipotassium glycyrrhizinate (GK2), and tranexamic acid (TXA) during the perioperative period, particularly by patients undergoing maxillomandibular fixation, which is a specific treatment used in dental and oral surgery. Specifically, the intraoral environment was assessed by testing saliva to investigate the effectiveness of this mouthwash during maxillomandibular fixation.

**Patients And Methods**

This study followed the 2010 Consolidated Standards for Reporting Trials (CONSORT) statement. The study was performed in line with the principles of the declaration of Helsinki. This study was approved by the Saga University Hospital Research Ethics Committee (Registration number 2019-07-01, date of registration 07/10/2019), and informed consent was obtained from all subjects and/or legally acceptable representative (LAR) of subjects to participate in the study. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (Registration number UMIN000046091, date of registration 17/11/2021). Single blind-participants are blinded parallel group was initiated inside a single facility.

The study subjects were patients in the Department of Dental and Oral Surgery of Saga University Hospital who required maxillomandibular fixation either after orthognathic surgery or for the treatment of mandibular fracture between October 2019 and March 2022. Patients with severe undernutrition (Alb ≤ 2.5 g/dl) or those who were unable to gargle unaided were excluded from the study (Table 1). During maxillomandibular fixation, they received transnasal enteral nutrition, with only water taken by mouth. The duration of fixation was 14–20 days. The subjects were allocated by the envelope method to either the HABITPRO group or the placebo group. The HABITPRO group gargled with a mouthwash containing
active ingredients (CPC, GK2, and TXA), and the placebo group with a mouthwash that did not contain any active ingredients. Both types of mouthwash were formulated so that there was no difference between them in factors such as color and taste. The procedure for intraoral cleaning started with mechanical cleaning with a water flosser (Waterpik, Water Pik, Inc., Colorado, USA) for approximately 5 minutes, followed by gargling with the allocated mouthwash. This cleaning was conducted 4 times a day after enteral nutrition, and the mouthwash was held in the mouth for 30 s before it was spat out. A mondamin automatic dispenser (Earth Corporation, Tokyo, Japan) was used to dispense 20 ml for each use.

**Evaluation Parameters**

(1) Assessment of plaque adhesion status using the Plaque Control Record

Plaque-disclosing dye (Shofu Inc., Kyoto, Japan) was used to dye all the tooth surfaces, and the state of plaque adhesion on the surface in the cervical region was scored.

(2) Measurements with a saliva analyzer (Sill-Ha, Arkray Marketing, Inc., Tokyo, Japan)

This device uses patients’ saliva to measure six parameters related to caries, periodontal disease, and oral cleanliness (carious bacteria, pH, acid buffering capacity, leukocyte count, protein levels, and ammonia levels). Specifically, saliva was collected after the mouth had been washed out with 3 ml of water for 10 s. Drops of saliva were placed on a special test paper, which was measured by the analyzer.

Measurements (1) and (2) were made at three time points: immediately before maxillomandibular fixation (baseline); on Day 10 of fixation; and immediately after fixation was released. There was individual variation between patients in the intraoral environment at baseline. Therefore, the amount of change in each measured value over time was calculated and compared. The primary outcome of this study was focused on PCR. Along with the primary outcome, six parameters related to caries, periodontal disease, and oral cleanliness in saliva were assessed. Regarding setting sample size, there are few similar research reports in the past. This study was conducted under the actual conditions of daily clinical practice, and the sample size was set as the number of possible cases within the study period.

**Statistical Analysis**

JMP version 14 was used for statistical analysis. The primary and secondary endpoints were compared between the HABITPRO and placebo groups. Student’s *t*-test was used for continuous variables, and Fisher’s exact test for nominal scales.

**Results**

As Figure 1 shows, 55 patients were enrolled in this study. A total of 55 patients who had undergone maxillomandibular fixation were randomly allocated to either a HABITPRO group (n = 29) or a placebo
group (n = 26). No side effects were observed in any group during the intervention. The study subjects were patients who required maxillomandibular fixation either after orthognathic surgery (n = 44) or for the treatment of mandibular fracture (n = 11). They included 24 men and 31 women, aged 16–81 years (mean age 28.11 years). PCR data were analyzed for 43 of the 55 patients from whom these data could be collected due to difficulty during maxillomandibular fixation (22 patients in the placebo group and 21 in the HABITPRO group).

1) There was no difference between the two groups in age or sex (Table 2). There were no reports of irritation-caused pain or signs of mucosal inflammation in either the HABITPRO group or the placebo group. No patient dropped out of the study early.

2) The ammonia level in saliva was measured with the Sill-Ha saliva analyzer, and the amount of change was calculated. The ammonia level was measured by the glutamate dehydrogenase assay. In the placebo group, the ammonia level after fixation release increased by +5.42 compared with baseline. In the HABITPRO group, a marked decrease of −14.66 was evident (Table 3). This difference between the two groups was significant.

3) The buffering capacity of saliva increased similarly by +4.11 compared with baseline in the placebo group, but decreased by −10.07 in the HABITPRO group. However, this difference between the two groups was not significant (Table 3).

4) There were no significant differences between the two groups in carious bacteria, leukocyte count, protein levels, or pH at any time point.

5) The PCR index varied widely at baseline. After fixation release, in the placebo group, the index increased by +24.61 compared with baseline, with an increase in the amount of plaque adhering to the teeth, whereas in the HABITPRO group, it was almost unchanged from baseline after fixation release, decreasing by −2.00 (Table 4). The difference between the two groups was significant (Figure 2).

Discussion

Recent years have seen rising interest in oral health management. PCR is one tool for this purpose. Although the rate of mouthwash use is not necessarily higher in Japan than in other countries, it has tended to increase in recent years. Initially, most people thought that mouthwash was used to eliminate bad breath, and it was often lumped together with fragrances, so that rather than using it regularly, people tended to use it occasionally in a way that was greatly removed from the goal of health management. Recently, however, it has gradually come to be thought of differently, as awareness has spread of the necessity of oral function management. The main uses of mouthwash now include washing out the mouth, retaining moisture, preventing caries and periodontal disease, and preventing bad breath.

The mouthwash investigated in this study is compounded with three medicinal ingredients. As a cationic surfactant, CPC exerts a bactericidal action by adsorption on the bacterial cell membrane, which
increases its fluidity and causes it to break down (Hwang et al., 2013; Ioannou et al., 2007). It is also believed to have a bactericidal effect by denaturing proteins. GK2 is a natural ingredient derived from licorice recognized for its anti-inflammatory properties, that is used to suppress stomatitis and throat inflammation (Michaelis et al., 2011). Additionally, it has been reported that GK2 inhibits inflammation and ameliorates colitis in mice (Vitali et al., 2013). TXA is an artificial synthetic amino acid that is expected to have hemostatic and anti-inflammatory actions (Kammerer et al., 2015; Jimenez et al., 2007). Recently, it has been reported that TXA mouthwash is effective for preventing postoperative bleeding after tooth extraction (Catter et al., 2018). Previously, efficacy of CPC-based mouthwash and CPC/TXA-based mouth rinse have been reported (Costa et al., 2013; Lee et al., 2017). Depending on the proportions in which these medications are combined, their pharmacological effects can cancel each other out, but it has been shown that the effects of all three medications in this mouthwash are all evident and do not cancel each other out. Additionally, CPC/GK2/TXA-based mouthwash inhibited propagation of the bacteria extracted from the post-surgical sutures after implant placement (Taninokuchi et al., 2021). In the present study, the effectiveness of this mouthwash was assessed in the specific environment resulting from maxillomandibular fixation. The results of the PCR experiments suggested that the use of a mouthwash containing active ingredients may suppress the adhesion of debris in comparison with the placebo group. During maxillomandibular fixation, all of the patients in this study carried out mechanical flossing with a Waterpik before using mouthwash. In both groups, the labial-side tooth surfaces and mucosa were thus adequately cleaned by mechanical stimulation, but the present results showed that this alone was insufficient. The ammonia level and buffering capacity of saliva were also affected by the mouthwash ingredients, despite Waterpik use. This may have been because the action of the Waterpik did not extend to the lingual-side tooth surfaces or the tongue and other parts of the mucosa. A previous study found that the use of this mouthwash reduced debris adhesion to the sutures used in implant surgery, which supports the present results (Taninokuchi et al., 2021). Salivary ammonia is thought to be generated by the metabolism of urea or amino acids by the ureases and amino acid-metabolizing enzymes of oral bacteria (Shu et al., 2007; Singer et al., 1983; Kanapka et al., 1983). Salivary ammonia concentration is associated with the total oral bacterial count, and Gram-negative bacilli produce particularly large amounts of ammonia. Gargling with this mouthwash effectively reduced the amount of ammonia in saliva, and it may significantly suppress these bacteria. The study subjects were generally young, with a mean age of 28 years, but the ammonia concentration in saliva has been shown to increase in accordance with age from age 40 years, which suggests that a greater effect might be obtained in older people. However, this is a topic for further study. Unlike oral medications, mouthwash use exerts a direct local action, but in consideration of its effect on the oral mucosa, the drug concentration should be kept quite low. This weakens its effectiveness, so that the actual effect of a single use is difficult to assess. Since this also reduces side effects, however, mouthwash has the advantages that it can be used continuously for a wide range of indications. The level of satisfaction with the mouthwash used in the present study was high, and it was readily accepted by patients from a wide range of age groups, from teenagers to older people. Barriers to mouthwash use include mucosal irritation and its smell and taste. Taste and color may thus be major factors in the
choice of mouthwash. Because preferences are such an individual matter, a more diverse range of flavors may become necessary in the future.

The importance of oral management in the perioperative period is now recognized in both medicine and dentistry, and active interventions are now being performed (Bergan et al., 2014; Soutome et al., 2017). However, what must not be forgotten is that gargling is the basis of oral hygiene management, and moreover that it is essential that this become a daily habit, so that patient education is important. Mouthwash use for oral hygiene management may be a factor in improving patients’ motivation and encouraging their willingness to continue. Mouthwash use can also be effective when normal oral cleaning is difficult, such as in times of disaster or in long-term care settings. It is generally marketed to prevent bad breath and is widely available for this purpose, but the type of mouthwash to be used must be chosen in light of its intended use. The mouthwash in the present study played a supplementary role in maintaining the oral environment after mechanical cleaning, and further improvements to its ingredients and composition are required. Of course, some active ingredients will give rise to cases of hypersensitivity. A certain percentage of adverse events is also known to occur as a result of povidone-iodine, benzethonium chloride, and other active ingredients that have been widely used.

During long-term use, cost is another issue that must be resolved alongside taste preferences and irritation. The development of a versatile mouthwash for use not just in the perioperative period will be very important in terms of meeting a social need.

Conclusions

The present results suggest that the continued use of a mouthwash containing active ingredients may suppress the deterioration of the oral environment to some extent, even in the specific environment resulting from maxillomandibular fixation. This mouthwash may therefore provide a tool for perioperative oral hygiene management.

Abbreviations

CPC, cetylpyridinium chloride; GK2, dipotassium glycyrrhizinate; TXA, tranexamic acid; PCR, plaque control record

Declarations

Ethics approval and consent to participate

This study was approved by the Saga University Hospital Research Ethics Committee (Approval number 2019-07-01, Registry time 07/10/2019). Informed consent was obtained from all subjects and/or legally acceptable representative (LAR) of subjects to participate in the study.

Consent for publication
Informed consent to publication of personal data was obtained from all patients/participants and/or their legally acceptable representatives.

**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information files.

**Competing interests**

The authors declare no competing interests.

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Not applicable.

**Authors' contributions**

Y.Y designed the study, R.A performed the experiments, all authors interpreted data, and Y.Y wrote the manuscript. All authors reviewed the manuscript.

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**References**


**Tables**

Tables 1 to 4 are available in the Supplementary Files section

**Figures**
Figure 1

Flow diagram of patients throughout the study
Figure 2

Representative intraoral photograph on day 10 of fixation and after fixation release.

Plaque-disclosing dye was used to dye all the tooth surfaces.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- mouthwashrawdateforBMC.xlsx
- Tables.docx