New oral hygiene care regimen reduces postoperative oral bacteria count and number of days with elevated fever in ICU patients with esophageal cancer

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Abstract: Using a controlled pre/post study design, we investigated the effects of professional mechanical cleaning of the oral cavity with benzethonium chloride, interdental brushes, and hydrogen peroxide on the number of oral bacteria and postoperative complications among esophageal cancer patients in an intensive care unit. Before surgery, 44 patients with esophageal cancer were recruited at Okayama Hospital from January through August 2015. The control group (n = 23) received routine oral hygiene care in the intensive care unit. The intervention group (n = 21) received intensive interdental cleaning with benzethonium chloride solution and tongue cleaning with hydrogen peroxide. The number of oral bacteria on the tongue surface and plaque index were significantly lower in the intervention group than in the control group on postoperative days 1 and 2 (P < 0.05). Additionally, the number of days with elevated fever during a 1-week period was significantly lower in the intervention group than in the control group (P = 0.037). As compared with routine oral hygiene, a new oral hygiene regimen comprising benzethonium chloride, interdental brushes, and hydrogen peroxide significantly reduced the number of oral bacteria and days with elevated fever in patients with esophageal cancer.

Keywords: Intensive care unit; oral hygiene; oral bacteria; postoperative complications; nurses.
Introduction

Esophageal cancer is a common cause of cancer death, and its incidence is increasing rapidly worldwide (1,2). Surgical treatment of esophageal cancer is usually invasive and thus may result in postoperative complications, the risk of which has not decreased (2). Because patients who develop postoperative complications have a high risk of postoperative death, it is essential to decrease the risk of such complications (3,4).

Pulmonary complications, including pneumonia, frequently develop after esophagectomy and are the most common reason for morbidity and mortality (5-7). Oral bacteria increase the risk of postoperative pneumonia in patients with esophageal cancer (8). Thus, preoperative reduction of oral bacteria is critical for this patient group (9,10). Preoperative dental brushing can reduce the risk of postoperative pneumonia in esophageal cancer patients (4,8). In addition, postoperative care that includes control of oral bacteria may greatly improve outcomes of esophageal surgery (11). In most intensive care units (ICUs) worldwide, postoperative oral hygiene care is performed by nurses. However, studies have not yet identified the optimal procedures and postoperative oral hygiene regimen to reduce oral bacteria in patients with esophageal cancer.

Dentists often use oral antiseptics for oral hygiene care. To reduce oral bacteria, chlorhexidine, povidone iodine, domiphen bromide, benzethonium chloride, benzalkonium chloride, fradiomycin sulfate, and sodium azulene sulfonate are widely used as major components in oral antiseptics (12). A systematic review reported that an oral hygiene regimen that included chlorhexidine antiseptic products reduced oral bacteria and the risk of ventilator-associated pneumonia in ICU patients, although evidence was limited for other antiseptics (13). However, the chlorhexidine concentration allowed for clinical use by Japanese government regulations is lower than that used in other countries (14); therefore, the expected effects have not been achieved. Benzethonium chloride is a widely used cationic surfactant of quaternary ammonium salts, has broad-spectrum antimicrobial activity for oral disinfection (15), and was thus investigated in this study.

Mechanical tooth cleaning is also used to reduce oral bacteria (16), and interproximal plaque removal is particularly important for oral hygiene. Use of interdental brushes with toothbrushes is recommended (17) because interdental brushes are more effective in removing plaque (18,19) and reducing gingival inflammation and periodontal pockets (20) as compared with an ordinary toothbrush alone or combined use of a toothbrush and dental floss or wood sticks (21). However, interdental brush use is not well established as oral hygiene care for inpatients (13).

A previous study showed that the combination of tongue cleaning and mechanical tooth cleaning was effective for improving the oral hygiene status of stroke patients in an ICU (22). In addition, ICU nurses generally use hydrogen peroxide to cleanse the oral mucosa (23). Although tongue cleaning with hydrogen peroxide may improve oral hygiene, the actual effects are unknown.

Here, we hypothesized that more-intensive oral hygiene care using benzethonium chloride, interdental brushes, and hydrogen peroxide would reduce the number of oral bacteria and risk of postoperative complications in patients with esophageal cancer. In this pre/post study of ICU patients with esophageal cancer, we investigated differences in the number of oral bacteria and rates of postoperative complications between patients who received a new intervention comprising professional mechanical cleaning of the oral cavity with benzethonium chloride, interdental brushes, and hydrogen peroxide and those who received routine oral hygiene care.

Materials and Methods

Study population

Fifty patients with a diagnosis of esophageal cancer were referred to the Division of Hospital Dentistry at Okayama Hospital during the period from January through August 2015 to receive professional mechanical tooth cleaning and scaling before surgery; 44 (88.0%) were recruited after excluding patients who transferred to another department or hospital, those who died before surgery, and those who declined surgery (Fig. 1).

Ethical considerations

This study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (No. 2261). Written informed consent was obtained from all patients who agreed to participate.

Design

The study design was a controlled pre/post study. After receiving professional mechanical tooth cleaning and scaling as preoperative care, the 44 patients were divided into two groups. The control group (n = 23) was recruited from January through April 2015, and the intervention group (n = 21) was recruited from May through August 2015. The control group received routine
oral hygiene care in the ICU, administered by nurses during postoperative days 1-3. The intervention group received more-intensive oral hygiene care, administered by dentists during postoperative days 1-3. Both regimens were performed three times a day (at 6:00, 14:00, and 21:00). The schedule is shown in Figure 2.

**The trial intervention**

**Routine oral hygiene care for the control group**

After aspirating phlegm and saliva in the oral cavity and around the tracheostomy tube or oropharyngeal tube, the patients underwent toothbrushing with an ordinary toothbrush and tongue cleaning with a sponge brush.

**Intensive oral hygiene care for the intervention group**

After performing the aspiration procedure described above, the intervention group underwent mechanical tooth cleaning with an ordinary toothbrush (ERAC510, LION Dental Products Company, Tokyo, Japan) and interdental brush (DENT. EX, LION Dental Products Company, Tokyo, Japan), with a 0.2% benzethonium chloride solution (Neostelin Green 0.2% mouthwash solution, Nippon Shika Yakuhin Co., Ltd, Yamaguchi, Japan) as antiseptic (15,24). In addition, patients received tongue cleaning with a sponge brush. A 0.3% hydrogen peroxide solution was used for mechanical cleansing but not for disinfection (25,26). The size of the interdental brush was individualized for the interdental space of each patient. The duration of the procedure was about 10 minutes.

**Data collection**

**Measurement of oral bacteria and oral hygiene status**

An oral examination was performed by one of five trained and calibrated dentists (S. M., H. M., A. T-T., A. Y., and T. M.) at 7:00-8:00 on the morning before surgery and on postoperative days 1-3 (Fig. 2).

Oral hygiene status was measured on the buccal side with a dental plaque index (PlI) (27). For the oral bacteria count, a dentist collected the tongue coating from the middle of the dorsum linguae. To obtain the samples, gentle pressure was used to wipe the tongue surface with a cotton swab, as directed by the manufacturer (28). The number of oral bacteria in the samples was immediately measured by a simple, portable bacteria counter (Panasonic Healthcare Co., Ltd., Tokyo, Japan) (28). The numbers of oral bacteria are presented as colony-forming units (log CFU/mL).

After completion of training, two volunteers recorded PlI and oral bacteria count and, to assess intra- and inter-examiner agreement, repeated the procedures within 1
week. The data were analyzed with the nonparametric κ test and intra-class correlation. The κ coefficients for intra- and inter-examiner and intra-class correlation coefficients were >0.8.

Data on systemic and oral health
Data on systemic and oral conditions were collected from medical and dental records. Measurements were performed before cancer therapy. The abstracted data included sex, age, type of cancer, cancer stage (International Classification of Diseases for Oncology ICD-10 version 2015), type of preoperative chemotherapy, surgical duration, amount of bleeding during surgery, type of reconstruction, Acute Physiology and Chronic Health Evaluation (APACHE) II score (29), predicted mortality based on APACHE II scores, Sequential Organ Failure Assessment (SOFA) scores (30), incidences of postoperative complications, intubation period, body temperature, number of days with elevated fever (≥38.0°C), length of stay in the ICU and hospital (31), medications, and oral condition (32).

Sample size estimation
The sample size was estimated with a statistical software package (nQuery Advisor, Statistical Solutions, Saugus, MA) and was based on the previously reported difference in PlI between control and intervention groups (22). A sample size of 19 per group was required for detection of a significant difference (90% power; two-sided significance level of 1.7%).

Data analysis
Data analysis was performed with the Statistical Package for the Social Science (SPSS version 19) (IBM, Tokyo, Japan). The chi-square test, Fisher exact test, or Mann-Whitney U test was used to compare data between the control and intervention groups. Statistical significance was defined as a P value of <0.05 or <0.017. Bonferroni-corrected P values were used to account for multiple comparisons.
roni correction was used for multiple comparisons of sequential changes (operative day vs postoperative day 1, operative day vs postoperative day 2, and operative day vs postoperative day 3).

The primary outcomes were number of oral bacteria during the ICU stay (number of oral bacteria on the tongue and PII). The secondary outcomes were postoperative complications (presence/absence of pneumonia, recurrent laryngeal nerve palsy, atelectasis, pulmonary edema, anastomotic leak, or elevated fever [≥38.0°C]), as determined by patient medical records.

**Results**

Table 1 shows the characteristics of the control and intervention groups. The overall cohort was predominantly male (>80%). The control group had a significantly higher rate of postoperative infection ($P = 0.044$). There were no other significant differences between the groups.

All patients received antibiotics and steroid therapy perioperatively. There was no significant difference between groups in the type of drug received (e.g., nonsteroidal anti-inflammatory drugs and acetaminophen).

Body temperature was significantly lower on postoperative days 1-3 than on the operative day in both groups ($P < 0.017$). In the intervention group, the number of oral bacteria on the tongue on postoperative days 2 and 3 and PII on postoperative day 2 were significantly lower than on the operative day ($P < 0.017$). During oral hygiene care in the ICU, body temperature did not significantly differ between groups on postoperative days 1-3 (Table 2). The number of oral bacteria on the tongue was significantly lower in the intervention group than in the control group on postoperative day 1 ($P < 0.017$). The PII was significantly lower in the intervention group than in the control group on postoperative days 1 and 2 ($P < 0.017$; Table 2).

Table 3 shows the rates of postoperative complications in the control and intervention groups. The number of days with elevated fever during a 1-week period was significantly lower in the intervention group than in the control group on postoperative days 1 and 2 ($P < 0.017$; Table 2).

**Discussion**

In this study, the PII score and number of oral bacteria were significantly lower in the intervention group than in the control group during the postoperative period in the

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**Table 2** Change in body temperature, number of bacteria, and plaque index in the ICU in the control and intervention groups

| Variable                          | Operative day | Postoperative day 1 | Postoperative day 2 | Postoperative day 3 |
|-----------------------------------|---------------|---------------------|---------------------|---------------------|
|                                   | Control group | Intervention group  | Control group       | Intervention group  | Control group       | Intervention group  |
| Body temperature (°C)             | n = 21        | n = 23              | $P$ value           | n = 21              | n = 23              | $P$ value           | n = 21              | n = 23              | $P$ value           |
|                                   |               |                     |                     |                     |                     |                     |                     |                     |                     |
|                                    | 36.5 (36.4, 37.0) | 36.4 (36.2, 36.6) | 0.267               | 38.3 (38.0, 38.5) | 38.4 (38.2, 38.7) | 0.157               | 38.3 (38.0, 38.7) | 38.1 (37.7, 38.3) | 0.157               | 38.0 (37.8, 38.2) | 37.7 (37.4, 37.9) | 0.023               |
| Number of oral bacteria on tongue (log CFU/mL) | n = 21       | n = 23               | $P$ value           | n = 21              | n = 23              | $P$ value           | n = 21              | n = 23              | $P$ value           |
|                                    | 7.2 (6.9, 7.4) | 7.3 (7.0, 7.5)      | 1.000               | 7.6 (7.2, 7.8)      | 7.1 (6.7, 7.4)     | 0.012               | 7.3 (6.8, 7.4)      | 6.7 (6.4, 6.9)     | 0.029               | 7.2 (6.6, 7.4) | 6.8 (6.4, 7.0) | 0.084               |
| Plaque index                       | n = 21        | n = 23               | $P$ value           | n = 21              | n = 23              | $P$ value           | n = 21              | n = 23              | $P$ value           |
|                                    | 0.2 (0.0, 0.3) | 0.1 (0.0, 0.2)      | 0.275               | 0.3 (0.2, 1.0)      | 0.1 (0.0, 0.3)     | 0.003               | 0.3 (0.2, 0.7)      | 0.0 (0.0, 0.1)     | <0.001              | 0.1 (0.0, 0.5) | 0.1 (0.0, 0.1) | 0.062               |

* Median (25th percentile, 75th percentile), † Mann-Whitney U test with Bonferroni correction (control group vs. intervention group).

**Table 3** Rates of postoperative complications in the control and intervention groups

| Variable                          | Control group | Intervention group |
|-----------------------------------|---------------|--------------------|
|                                   | n = 21        | n = 23             | $P$ value‡          |
| Recurrent laryngeal nerve palsy    | 5 (23.8)*     | 8 (34.8)           | 0.426               |
| Pneumonia                         | 4 (19.0)      | 1 (4.3)            | 0.176               |
| Atelectasis                       | 14 (66.7)     | 18 (78.3)          | 0.300               |
| Pulmonary edema                   | 21 (100.0)    | 23 (100.0)         | –                   |
| Anastomotic leak                  | 3 (14.3)      | 5 (21.7)           | 0.404               |
| Number of days with elevated fever (≥38.0°C) during a 1-week period | 4.0 (2.0, 5.0)* | 2.0 (1.0, 2.5) | 0.037               |

* $n$ (%), † median (25th percentile, 75th percentile), ‡ chi-square test, Fisher exact test, or Mann-Whitney U test.
ICU. The oral care regimen for the intervention group included benzethonium chloride for oral disinfection (15,24) and mechanical tooth cleaning with interdental brushes, to remove interproximal plaque (17). This method appears to qualitatively improve postoperative oral hygiene care for patients with esophageal cancer.

The median number of days with elevated fever (≥38.0°C) during a 1-week period was significantly lower in the intervention group than that in the control group. Systemic inflammatory response syndrome is induced by highly invasive surgery, wound infection, and drug-induced hepatic injury and is a major factor in postoperative fever induction in esophageal cancer patients (33-35). Because of the significant difference in the rate of postoperative infection between the intervention and control groups, we reanalyzed the data after excluding cases of postoperative infection (n = 4). The result was unchanged (data not shown). There was no significant difference between the groups in type of surgery or other perioperative conditions. All patients received antibiotics and steroid therapy during the perioperative period, and the type of drug received did not differ between groups. In Okayama University Hospital, the use of antibiotics and steroids is governed by a standardized protocol. The difference in the number of days with elevated fever may be related to a reduction in oral bacteria by the intensive oral hygiene care, which could have reduced the infection rate. Recurrent laryngeal nerve paralysis is a major postoperative complication in esophageal cancer patients (36) and can cause silent aspiration (37), which contributes to elevated fever. However, because the incidence of recurrent laryngeal nerve palsy did not significantly differ between groups, its differential effects on elevated fever in this study were likely small.

Pneumonia incidence was lower in the intervention group (4.3%) than in the control group (19.0%), but the difference was not significant. A previous review noted that postoperative pneumonia was a common complication of general surgical procedures (incidence, 0.5-28%) (7). Because the incidence of pneumonia in the present control group was within the previously reported range and not high, our analysis was unlikely to detect a significant difference between the groups, because of the floor effect.

To reduce the number of oral bacteria, the intervention group received additional mechanical interdental cleaning with benzethonium chloride solution and tongue cleaning with hydrogen peroxide. Previous studies have investigated oral hygiene regimens for ICU patients, including mechanical tooth cleaning with a toothbrush and use of antiseptics; however, oral hygiene care methods are not standardized worldwide (38-40). A previous study found that the combination of tongue cleaning and mechanical tooth cleaning with a toothbrush and use of an interdental brush and chlorhexidine improved the oral hygiene status of stroke patients in ICUs (22). Our findings are consistent with these previous results. Furthermore, we modified the tongue cleaning procedure by using a 0.3% hydrogen peroxide solution for mechanical cleansing but not for disinfection (25,26), which may have reduced the number of bacteria. In this study, we made minor changes to the routine care provided by ICU nurses and demonstrated that the present oral hygiene regimen is feasible and beneficial for esophageal cancer patients.

In this study, dentists performed the new oral hygiene regimen in a research setting. However, nurses can provide the same care in a clinical setting. Because nurses perform postoperative oral hygiene care in most ICUs worldwide, we believe that they should be trained to perform this new oral hygiene regimen.

This study has several limitations. First, it enrolled a small number of participants at a single center. Second, the relationship between elevated fever and the number of oral bacteria remains unclear. Therefore, further large-scale studies are needed in order to confirm our findings. Third, the intervention was performed by dentists and routine oral hygiene care was provided by nurses. The differences in the skills of dentists and nurses in performing oral hygiene care should be considered. However, the new oral hygiene regimen does not require specialized skills and thus the effects of differences in clinical skill are likely to be small.

In conclusion, as compared with routine oral hygiene care, a new postoperative oral hygiene regimen comprising interdental cleaning with benzethonium chloride solution and tongue cleaning with hydrogen peroxide significantly reduced the number of oral bacteria on the tongue and teeth and the median number of days with elevated fever in patients with esophageal cancer.

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Conflict of interest

None declared.
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