### Title

Efficacy of topical antibiotic administration on the inhibition of perioperative oral bacterial growth in oral cancer patients: a preliminary study

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Efficacy of topical antibiotic administration on the inhibition of perioperative oral bacterial growth in oral cancer patients: a preliminary study


Abstract. Parenteral antibiotic prophylaxis is the current standard of therapy in clean-contaminated oral cancer surgery. Nevertheless, the incidence of surgical site infection (SSI) in oral oncological surgery is relatively high, especially in major surgery with reconstruction and tracheostomy. The aims of this study were to investigate the perioperative condition related to microorganisms in the oral cavity and to examine the efficacy of the topical administration of tetracycline in reducing the number of bacteria in the oropharyngeal fluid during intubation. The number of oral bacteria was measured during intubation in patients undergoing major oral cancer surgery. The efficacy of the topical administration of tetracycline or povidone iodine gel in reducing the bacteria was then investigated. Bacteria in the oropharyngeal fluid grew from $10^6$ CFU/ml to $10^8$ CFU/ml during the 3 h after intubation (CFU, colony-forming units). When tetracycline was applied to the dorsum of the tongue, oral bacteria decreased immediately to $10^5$ CFU/ml, and the number of bacteria in the oropharyngeal fluid was maintained below $10^7$ CFU/ml for 7 h. The concentration of tetracycline in the oropharyngeal fluid was extremely high for several hours after topical administration. The topical administration of tetracycline could reduce oral bacteria in patients undergoing clean-contaminated oral cancer surgery. This method is expected to be effective in the prevention of SSI.

Keywords: surgical site infection; topical administration of antibiotics; oral cancer surgery; oral care; oral bacteria.

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Postoperative infection, including surgical site infection (SSI) or remote infection, occurs frequently after head and neck cancer surgery, causing not only a prolonged hospital stay and decrease in quality of life, but also a poorer prognosis due to the delay in postoperative treatment. According to the guidelines for the prevention of SSI published by the US Centers for Disease Control and Prevention (CDC) in 1999, various factors such as age, nutritional status, diabetes,
smoking, and obesity are thought to be related to the occurrence of SSI. The CDC guidelines state that the risk of SSI can be conceptualized as a level of bacterial contamination × virulence/resistance of the host patient, and that if a surgical site is contaminated with >10^5 microorganisms per gram of tissue, the risk of SSI is markedly increased.

The number of microorganisms in the saliva usually exceeds 10^5 CFU/ml (CFU, colony-forming units). The CDC guidelines classify surgical wounds by degree of contamination as follows: class 1, clean; class 2, clean-contaminated; class 3, contaminated; and class 4, dirty-infected. According to the CDC guidelines, wounds in the oral cavity and oropharynx are included in the class 2 category, and the leading cause of the development of SSI in oral cancer surgery appears to be perioperative contamination by microorganisms in the saliva.

Parenteral antibiotic prophylaxis is the current standard of therapy in clean-contaminated oncological head and neck surgery. Nevertheless, the reported incidence of SSI in head and neck surgery is relatively high, ranging from 10.9% to 45.0%. Some studies in normal, healthy volunteers have documented the efficacy of a single dose of antibiotic mouthwash in quantitatively reducing aerobic and anaerobic bacteria in the oral cavity for 4 h. However, in a study on head and neck surgery with flap reconstruction, Simons et al. reported that the additional use of topical piperacillin/tazobactam administered as a mouthwash immediately before surgery, and once a day for 2 days postoperatively, did not appear to enhance the prophylactic benefit of parenteral antibiotics alone.

The objectives of the present study were to investigate the perioperative condition related to microorganisms in the oral cavity and to examine the efficacy of the topical administration of tetracycline ointment and iodine gel in reducing the number of bacteria in the oral fluid.

**Materials and methods**

A total of 25 subjects were recruited into this study (Table 1).

**Number of bacteria in the oral cavity during surgery**

After intubation, the oral cavities of five patients who were to undergo neck dissection were irrigated with 500 ml of saline. Ampicillin/sulbactam (1500 mg) was administered parenterally at the start of surgery. The number of bacteria on the surfaces of the dorsum of the tongue, buccal mucosa, and hard palate, and in the oropharyngeal fluid, was measured every 15 min until the neck dissection had been completed.

**Efficacy of the topical administration of povidone iodine gel or tetracycline ointment on the inhibition of bacterial growth in the oral cavity during surgery**

The oral cavities of 10 patients undergoing neck dissection were irrigated with saline, as described above, after intubation. Patients were divided randomly into two treatment groups: (1) parenteral ampicillin/sulbactam plus topical administration of 10 g of 10% povidone iodine gel on the dorsum of the tongue (five patients), and (2) parenteral ampicillin/sulbactam plus topical administration of 10 g of 3% tetracycline ointment on the tongue (five patients). The number of bacteria on the surface of the tongue and in the oropharyngeal fluid was measured every 15 min until the neck dissection had been completed.

**Efficacy of topical tetracycline ointment on the inhibition of bacterial growth in the oral cavity after surgery**

Ten patients who underwent oral cancer surgery with flap reconstruction and were managed under intubation by tracheotomy, had their oral cavity irrigated with 200 ml of water and were divided randomly into two treatment groups: (1) parenteral administration of 1500 mg of ampicillin/sulbactam three times a day (five patients), and (2) parenteral

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**Table 1. Patient characteristics in the three studies.**

<table>
<thead>
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<th>Study 1 (during surgery)</th>
<th>Study 2 (during surgery)</th>
<th>Study 3 (in the ICU)</th>
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<tr>
<td>Stage IV</td>
<td>4</td>
<td>4</td>
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<td></td>
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<tr>
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</table>

ICU: intensive care unit.
ampicillin/subactam plus topical admin-
istration of 10 g of 3% tetracycline oint-
ment on the tongue on the day after
surgery (five patients). The number of
bacteria on the surface of the tongue
and in the oropharyngeal fluid was mea-
sured every 30 min for 8 h.

The concentration of tetracycline in the
oropharyngeal fluid was measured in a
patient undergoing neck dissection during
surgery, before topical administration, and
at 5 min, 1, 2, and 5 h after topical admin-
istration, with a bioassay. This study was
approved by the university ethics com-
mittee.

Results

Number of bacteria in the oral cavity
during surgery (Fig. 1)
The bacterial count on the tongue and in
the oropharyngeal fluid increased gradu-
ally. The number of bacteria in the or-
opharyngeal fluid exceeded 10^7 CFU/ml
after 30 min, while on the tongue the
number exceeded 10^3 CFU/ml after 2 h.
In contrast, the number of bacteria on the
buccal mucosa and the hard palate did not
increase within the measurement time.

Efficacy of the topical administration of
povidone iodine gel or tetracycline
ointment on the inhibition of bacterial
growth in the oral cavity during surgery
(Fig. 2)

In patients administered topical povidone
iodine, the number of bacteria on the
tongue remained below 10^3 CFU/ml for
approximately 150 min. However, bacte-
ria in the oropharyngeal fluid multiplied at
a rate similar to the control group, which
indicated that topical povidone iodine did
not inhibit the growth of oral bacteria.

In contrast, after the topical administra-
tion of tetracycline ointment, the number of
oral bacteria remained below baseline
both on the tongue and in the oropharyn-
geal fluid throughout the operation. The
efficacy of topical tetracycline on the inhi-
bition of oral bacteria was apparent for
up to 150 min.

Efficacy of topical tetracycline ointment
on the inhibition of bacterial growth in
the oral cavity after surgery (Fig. 3)

In the control group, oral bacteria in-
creased rapidly after irrigation of the oral
cavity. The number of bacteria in the
oropharyngeal fluid reached 10^8 CFU/ml
approximately 150 min later, and the
number on the tongue was more than 10^7 CFU/
ml 2 h later. It was thought that the level of
oral bacteria in the control group had
increased to a level high enough to repre-
sent a great risk of SSI, so measurements
were stopped and irrigation was per-
formed.

In contrast, the number of oral bacteria
was reduced to less than baseline both on
the tongue and in the oropharyngeal fluid
at 30 min after the topical administration
of tetracycline ointment. The number of
bacteria on the tongue remained below
10^6 CFU/ml for up to 7 h after the topical
administration of tetracycline ointment.
The bacterial count in the oropharyngeal
fluid increased gradually, but remained
below 10^6 CFU/ml for up to 5 h and below
10^5 CFU/ml for up to 7 h after topical
administration.

The concentration of tetracycline in the
oropharyngeal fluid was 1.70 µg/ml at
5 min, 89.3 µg/ml at 1 h, and 183.4 µg/
ml at 2 h after application, and was main-
tained at 89.3 µg/ml up to 5 h after appli-
cation.

A SSI occurred in a patient in the con-
trol group, but there was no case of SSI in
those receiving topical tetracycline.

Discussion

SSI occurs frequently in patients with head
and neck cancer who undergo clean-con-
taminated surgery, particularly when fol-
lowed by flap reconstruction. The reported
rate of SSI in head and neck oncological
surgery ranges from 10.9% to 45.0%.10–12
Various risk factors for SSI in head and
neck surgery have been investigated pre-
viously (Table 2). These include patient
characteristics such as age, sex, diabetes,
body mass index (BMI), American Soci-
ety of Anesthesiologists (ASA) score,
smoking habit, drinking habit, nutrition,
prolonged hospital stay, and undergoing
preoperative chemotherapy, as well as
operative characteristics such as operation
time, blood loss, blood transfusion, recon-
structive surgery, and preoperative radio-
therapy. However, the relationship
between these factors and the frequency
of SSI remains controversial. Despite this,
most investigators have stated that trache-
otomy and clean-contaminated surgery
are highly related to the incidence of SSI.

Coskun et al. first described tracheo-
tomy as an important factor that may be
responsible for higher postoperative
wound infection rates.10 Many investiga-
tors later demonstrated the statistical
significance of this relationship, although
the underlying reasons to explain this signifi-
cance remain to be clarified.3–6,11 The pre-
sent study found that the number of oral
bacteria increased immediately after intu-
bation or tracheotomy, and this may be the
cause of the high occurrence of SSI in
patients with a tracheotomy.

Clean-contaminated procedures in head
and neck surgery may be associated with a
high risk of postoperative wound infection
unless adequate antimicrobial prophylaxis
is applied.10 Without the use of perioper-
ative antibiotics, SSI rates may reach up to
80% after this type of procedure.16 How-
ever, even after antimicrobial prophylaxis,
postoperative wound infection rates in
clean-contaminated head and neck surgery
are higher than those in other types of
procedures.3–7 Coskun et al. reported that
prolonged and 1-day antibiotic regimens for both clean and clean-contaminated procedures were similar in efficacy for preventing SSI, being 7% vs. 3% for clean procedures and 30% vs. 28% for clean-contaminated procedures. Simons et al. reported that the most important variable in the development of SSI in head and neck surgery appeared to be perioperative contamination of the normally sterile neck sites with the oropharyngeal flora contained in the saliva. Grandis et al. reported that clindamycin mouthwash was highly effective in reducing oral bacteria but that parenterally administered clindamycin was less effective. In a series of preliminary trials, they demonstrated that topical antibiotic prophylaxis using a single dose of clindamycin administered as a preoperative mouthwash, combined with intraoperative antibiotic irrigation and a single post-operative mouthwash, was effective in patients undergoing laryngectomy and neck dissection. Based on these results, Simons et al. performed a randomized, prospective clinical trial on the efficacy of topical antibiotic prophylaxis in patients undergoing contaminated head and neck surgery with flap reconstruction. They divided patients into two groups: (1) parenteral piperacillin/tazobactam, and (2) piperacillin/tazobactam plus topical piperacillin/tazobactam administered as a mouthwash immediately before surgery and once a day for 2 days postoperatively. Their results showed that the addition of topical piperacillin/tazobactam did not enhance the prophylactic benefit of parenteral antibiotics alone. Since these studies, topical antibiotic prophylaxis for SSI has not been investigated in head and neck oncology surgery.

Minimizing the oral and oropharyngeal bacteria may play an essential role in preventing SSI in oral cancer surgery. The present study showed the number of bacteria on the dorsum of the tongue and in the oropharyngeal fluid to increase immediately after intubation during surgery. This increase is thought to be due to the loss of swallowing and self-cleaning functions during general anaesthesia. The failure of the antibiotic mouthwash to prevent SSI in head and neck surgery in the prospective study by Simons et al. may have been due to the focus on preoperative oral cleaning.

The rapid increase in oral bacteria after intubation shows that the parenteral administration of antibiotics alone is insufficient to prevent oral bacterial growth. The present study was conducted because it was hypothesized that the topical application of povidone iodine or tetracycline to the oral cavity would reduce the number of bacteria in the oropharyngeal fluid. Although oral topical chlorhexidine application is used widely to prevent ventilator-associated pneumonia (VAP) in Western countries, the application of chlorhexidine to the mucous membranes is prohibited in Japan because there was a case of anaphylactic shock. Parenteral and topical administration may exert their effects by different mechanisms; topical povidone iodine or tetracycline in the oral cavity may sterilize the oropharyngeal fluid, while parenteral antibiotics may exert their effect by being directly present at the operative site. The results of the present study indicated that the topical application of povidone iodine gel was not effective, probably due to the low concentration in the oropharyngeal fluid. On the other hand, the topical administration of

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**Fig. 2.** Efficacy of topical povidone iodine gel and tetracycline ointment on the reduction of oral bacterial growth during intubation. The growth of bacteria on the tongue was slightly suppressed by the topical administration of iodine, and markedly suppressed by tetracycline ointment (A). In the oropharyngeal fluid, there was no inhibition of bacterial growth by topical povidone iodine gel, while after the topical administration of tetracycline ointment, oral bacteria decreased markedly, and this was maintained for at least 165 min after intubation (B).

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The number of bacteria before and after the administration of povidone iodine and tetracycline in the oropharyngeal fluid and tongue is shown in the graph. The graph indicates that the number of bacteria decreased significantly after the administration of these substances.
Fig. 3. Efficacy of topical tetracycline ointment on the reduction of oral bacterial growth after surgery during respiratory management by tracheostomy. The number of oral bacteria was less than baseline both on the tongue and in the oropharyngeal fluid 30 min after the topical administration of tetracycline ointment. The bacterial count on the tongue was maintained at below 10⁵ CFU/ml for up to 7 h, while that in the oropharyngeal fluid was maintained at below 10⁶ CFU/ml for up to 5 h and at below 10⁷ CFU/ml for up to 7 h after topical administration.

tetracycline ointment showed excellent efficacy on the reduction of oral bacteria. Topical antibiotics also reduced bacteria on the tongue and in the oropharyngeal fluid for up to 7 h in postoperative tracheotomy patients. Although the level of tetracycline was only tested in one subject during surgery, the concentration of tetracycline in the oropharyngeal fluid was between 89.3 and 183.4 µg/ml for up to 5 h after intubation, which is a hundred-fold or more times higher than the minimum inhibitory concentration (MIC) of tetracycline for most oral bacteria. The sustainment of such a high concentration for a long period of time was likely due to the loss of swallowing function during intubation.

Table 2. Summary of risk factors for surgical site infection in head and neck surgery reported in the previous literature.*

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<td>128/697 (18.4%)</td>
<td>112/276 (40.6%)</td>
<td>21/209 (10.0%)</td>
<td>100/258 (38.8%)</td>
<td>117/260 (45.0%)</td>
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SSI, surgical site infection; BMI, body mass index; ASA, American Society of Anesthesiologists.

*S*, significant; NS, not significant; NE, not examined.
The administration of non-absorbable oral antimicrobial agents in divided doses on the day before elective colorectal surgery is strongly recommended in the CDC guidelines for the prevention of SSI. Similar to colorectal surgery, it is likely that topical, as well as parenteral, antibiotic administration is necessary to prevent SSI in head and neck clean-contaminated surgery. The results obtained in the present study suggest that the topical administration of tetracycline ointment may reduce SSI in oral cancer patients who undergo extensive surgery with flap reconstruction and tracheotomy. However, some problems remain to be resolved before this method of prophylaxis can be applied clinically. First, the most appropriate antibiotics for topical administration should be determined. The pathogenic bacteria in clean-contaminated head and neck surgery SSI are *Staphylococcus aureus*, streptococci, and oropharyngeal anaerobes (e.g., peptostreptococci). Tetracycline has a strong antibacterial activity on *S. aureus* and streptococci, and intermediate activity on oropharyngeal peptostreptococci; however, tetracycline has only weak activity on *Pseudomonas aeruginosa*, and in recent times the number of tetracycline-resistant bacteria has increased. Tetracycline should only be applied within the SSI high-risk period, 48 h postoperatively, to avoid the emergence of resistant bacteria. Second, this was a preliminary study with a small number of patients and the results were not analysed statistically. The present study demonstrated the reduction of oropharyngeal bacteria by topical administration of tetracycline, but whether the frequency of SSI is reduced by topical antibiotics remains unclear. Future studies should focus on patient outcome measures rather than bacterial counts.

**Patient consent**
Not required.

**References**


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**Competing interests**
None.

**Ethical approval**
Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences; No. 1497.

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