

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

M. Funahara¹, S. Hayashida¹,
Y. Sakamoto¹, S. Yanamoto¹,
K. Kosai², K. Yanagihara²,
M. Umeda¹

¹Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan;

²Department of Laboratory Medicine, Nagasaki University Graduate School of Medicine, Nagasaki, Japan

M. Funahara, S. Hayashida, Y. Sakamoto, S. Yanamoto, K. Kosai, K. Yanagihara, M. Umeda: Efficacy of topical antibiotic administration on the inhibition of perioperative oral bacterial growth in oral cancer patients: a preliminary study. *Int. J. Oral Maxillofac. Surg.* 2015; 44: 1225–1230. © 2015 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

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 tracheotomy. 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.

Accepted for publication 2 June 2015
Available online 26 June 2015

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.¹ The CDC guidelines state that the risk of SSI can be conceptualized as a level of bacterial contamination \times 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.² Nevertheless, the reported incidence of SSI in head and neck surgery is relatively high, ranging from 10.9% to 45.0%.³⁻¹⁰ 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.^{11,12} 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.¹³

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 and resection of the intraoral tumour was started. The number of bacteria was measured with a rapid oral bacteria quantification system (Panasonic Healthcare Co. Ltd., Osaka, Japan) using the dielectrophoresis and impedance measurement method.^{14,15} Because the detection limit of this machine is

10^5 CFU/ml, actual bacterial counts less than this limit were displayed as 10^5 CFU/ml.

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

Table 1. Patient characteristics in the three studies.

	Study 1 (during surgery)	Study 2 (during surgery)	Study 3 (in the ICU)
Age, mean (range), years	76.2 (67-93)	65.2 (52-75)	66.2 (51-76)
Gender			
Male	3	7	8
Female	2	3	2
Primary site			
Tongue	1	5	5
Mandibular gingiva	2	0	1
Maxillary gingiva	1	2	1
Buccal mucosa	1	0	0
Floor of the mouth	0	3	3
Stage			
Stage II (late neck metastasis)	1	2	0
Stage III	0	4	2
Stage IV	4	4	8
Surgery			
Neck dissection	1	2	0
Neck dissection + tumour resection	3	2	2
Neck dissection + tumour resection + reconstruction	1	6	8
Tracheotomy			
Yes	3	8	10
No	2	2	0
Total	5	10	10

ICU, intensive care unit.

ampicillin/sulbactam plus topical administration of 10 g of 3% tetracycline ointment 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 measured 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 administration, with a bioassay.

This study was approved by the university ethics committee.

Results

Number of bacteria in the oral cavity during surgery (Fig. 1)

The bacterial count on the tongue and in the oropharyngeal fluid increased gradually. The number of bacteria in the oropharyngeal fluid exceeded 10^7 CFU/ml after 30 min, while on the tongue the number exceeded 10^7 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 10^7 CFU/ml for

approximately 150 min. However, bacteria 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 administration of tetracycline ointment, the number of oral bacteria remained below baseline both on the tongue and in the oropharyngeal fluid throughout the operation. The efficacy of topical tetracycline on the inhibition 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 increased 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 represent a great risk of SSI, so measurements were stopped and irrigation was performed.

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 10^7 CFU/ml for up to 7 h after topical administration.

The concentration of tetracycline in the oropharyngeal fluid was $1.70 \mu\text{g/ml}$ at 5 min, $89.3 \mu\text{g/ml}$ at 1 h, and $183.4 \mu\text{g/ml}$ at 2 h after application, and was maintained at $89.3 \mu\text{g/ml}$ up to 5 h after application.

A SSI occurred in a patient in the control 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-contaminated surgery, particularly when followed by flap reconstruction. The reported rate of SSI in head and neck oncological surgery ranges from 10.9% to 45.0%.³⁻¹⁰ Various risk factors for SSI in head and neck surgery have been investigated previously (Table 2). These include patient characteristics such as age, sex, diabetes, body mass index (BMI), American Society 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, reconstructive surgery, and preoperative radiotherapy. However, the relationship between these factors and the frequency of SSI remains controversial. Despite this, most investigators have stated that tracheotomy and clean-contaminated surgery are highly related to the incidence of SSI.

Coskun et al. first described tracheotomy as an important factor that may be responsible for higher postoperative wound infection rates.¹⁰ Many investigators later demonstrated the statistical significance of this relationship, although the underlying reasons to explain this significance remain to be clarified.^{3-6,8} The present study found that the number of oral bacteria increased immediately after intubation 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 perioperative antibiotics, SSI rates may reach up to 80% after this type of procedure.¹⁶ However, even after antimicrobial prophylaxis, postoperative wound infection rates in clean-contaminated head and neck surgery are higher than those in other types of procedures.¹⁷ Coskun et al. reported that

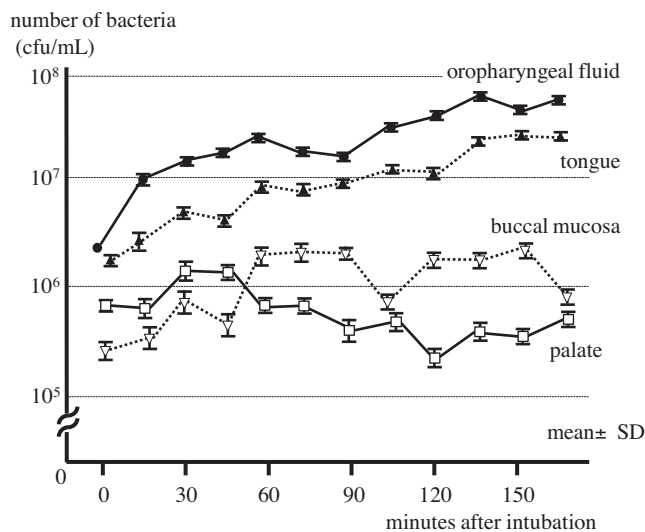


Fig. 1. Growth of oral bacteria during surgery. Bacteria in the oropharyngeal fluid and on the tongue increased rapidly after intubation, whereas bacteria on the buccal mucosa and the palate did not.

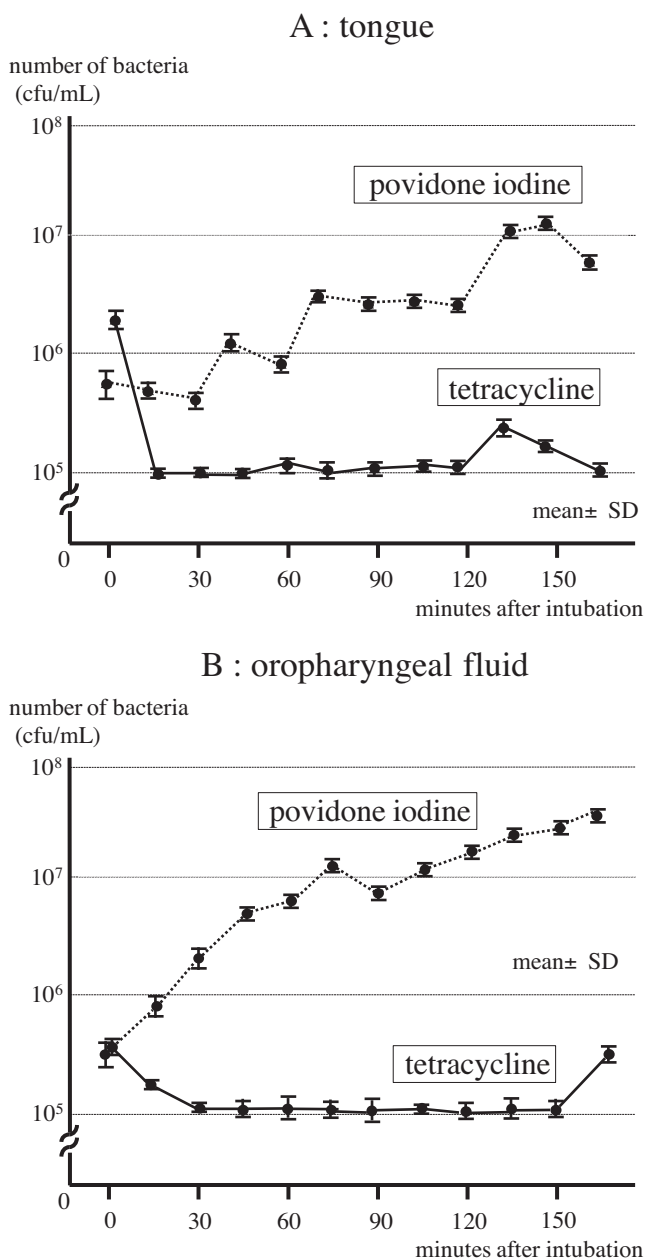


Fig. 2. Efficacy of topical povidone iodine gel and tetracycline ointment on the reduction of oral bacterial growth during intubation. The growth of bacteria on the tongue was slightly suppressed by the topical administration of iodine, and markedly suppressed by tetracycline ointment (A). In the oropharyngeal 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).

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.¹⁰

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.¹³ Grandis et al. reported that clindamycin mouthwash was highly effective in reducing oral bacteria but that parenterally administered clindamycin was less effective.¹⁸ 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.¹³ 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,¹⁹ 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

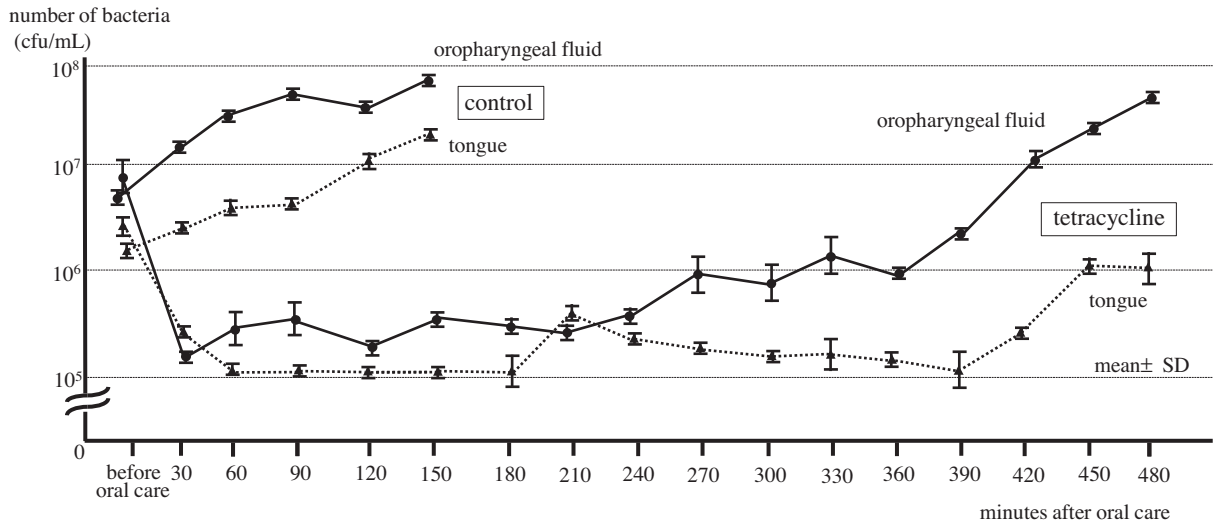


Fig. 3. Efficacy of topical tetracycline ointment on the reduction of oral bacterial growth after surgery during respiratory management by tracheotomy. The number of oral bacteria was less than baseline both on the tongue and in the oropharyngeal fluid 30 min after the topical administration of tetracycline ointment. The bacterial count on the tongue was maintained at below 10⁶ 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.²⁰ 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.^a

Author (year)	Cunha (2012) ³	Lee (2011) ⁴	Karakida (2010) ⁵	Ogihara (2009) ⁶	Lotfi (2008) ⁷	Penel (2005) ⁸	Cloke (2004) ⁹
Focus	Head and neck surgery	Major oncological surgery	Flap reconstruction	Oncological surgery	Clean-contaminated	Clean-contaminated	Free flap reconstruction
Frequency of SSI	15/137 (10.9%)	128/697 (18.4%)	112/276 (40.6%)	21/209 (10.0%)	100/258 (38.8%)	117/260 (45.0%)	21/100 (21.0%)
Risk factor							
Age	(NE)	(NE)	NS	NS	NS	NS	NS
Sex	(NE)	(NE)	NS	NS	NS	S*	(NE)
Smoking	NS	S*	NS	NS	S*	NS	NS
Drinking	NS	S*	NS	NS	NS	NS	(NE)
Diabetes	NS	S*	(NE)	NS	(NE)	(NE)	(NE)
BMI	NS	NS	NS	NS	(NE)	NS	(NE)
ASA score	NS	NS	S*	NS	(NE)	NS	(NE)
Anaemia	S*	S*	(NE)	(NE)	(NE)	(NE)	(NE)
Hypoalbuminemia	(NE)	S*	(NE)	(NE)	(NE)	NS	(NE)
Primary site	(NE)	S*	(NE)	(NE)	(NE)	S*	(NE)
Preoperative radiotherapy	S*	S*	(NE)	NS	NS	NS	(NE)
Preoperative chemotherapy	NS	S*	NS	S*	(NE)	S*	(NE)
Previous surgery	S*	(NE)	(NE)	(NE)	NS	NS	(NE)
Surgical procedure	NS	S*	S*	(NE)	(NE)	NS	(NE)
Advanced stage	(NE)	S*	S*	S*	S*	NS	(NE)
Blood transfusion	S*	S*	S*	(NE)	(NE)	(NE)	NS
Duration of surgery	S*	S*	S*	S*	S*	NS	NS
Flap reconstruction	NS	S*	(NE)	S*	S*	NS	(NE)
Blood loss	(NE)	(NE)	S*	S*	(NE)	NS	(NE)
Tracheotomy	S*	S*	S*	S*	NS	S*	(NE)
Clean-contaminated	(NE)	S*	(NE)	S*	(NE)	(NE)	(NE)
Preoperative hospital stay	S*	(NE)	(NE)	(NE)	(NE)	S*	NS

SSI, surgical site infection; BMI, body mass index; ASA, American Society of Anesthesiologists.

^aS*, 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.

Funding

None.

Competing interests

None.

Ethical approval

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

Patient consent

Not required.

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Address:

Madoka Funahara
Department of Clinical Oral Oncology
Nagasaki University Graduate School of
Biomedical Sciences
1-7-1 Sakamoto
Nagasaki 852-8588
Japan
Tel.: +81 95 819 7698
E-mail: bb55312902@cc.nagasaki-u.ac.jp