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Prevention of surgical site infection after oral cancer surgery by topical tetracycline

Results of a multicenter randomized control trial

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Abstract

Background: In a pilot study, we showed that topical administration of a tetracycline could decrease oral bacteria levels for 6 hours in patients who underwent oral cancer surgery combined with tracheotomy and flap reconstruction. This multicenter, randomized control trial aimed to investigate the effectiveness of topical application of tetracycline ointment for prevention of surgical site infection (SSI) associated with major oral cancer surgery.

Methods: One hundred seventeen patients who underwent oral cancer resection combined with neck dissection, flap reconstruction, and tracheotomy were divided randomly into an intervention group (n = 56) and a control group (n = 61). The intervention consisted of topical administration of tetracycline ointment on the dorsum of the tongue every 6 hours for 48 hours postoperatively. Factors relating to the occurrence of SSI in both groups were subjected to logistic regression analysis.

Results: SSI occurred in 11 patients (19.6%) in the intervention group and 22 patients (36.1%) in the control group. Multivariate analysis showed that a longer operating time and not receiving topical tetracycline were independent risk factors for development of SSI.

Conclusion: Administration of topical tetracycline for 48 hours postoperatively is an effective way of preventing SSI after oral cancer surgery.

Abbreviations: CDC = Centers for Disease Control and Prevention, RCT = randomized control trial, SSI = surgical site infection.

Keywords: oral cancer, randomized control trial, surgical site infection, tetracycline

1. Introduction

Despite recent advances in antibiotic therapy, surgical site infection (SSI) after major oncologic surgery of head and neck cancer continues to occur at an unacceptable rate, and remains one of the most frequent postoperative complications.[1–8] The reasons for the high incidence of SSI are thought to include not only surgical technique and poor preoperative nutrition but also the presence of pathogenic microorganisms in the oral cavity. Furthermore, patients with oral cancer who undergo tumor resection combined with reconstructive surgery and tracheotomy have higher than normal levels of bacteria in the oropharyngeal fluid because of swallowing disturbance and reduced self-cleaning in the oral cavity.[9]

Use of topical antibiotic prophylaxis for SSI has been investigated in various types of surgery,[10] but not as yet in head and neck surgery. We previously reported that the number of bacteria in oropharyngeal fluid increased to more than 100-fold in patients receiving mechanical ventilation by oral intubation or tracheotomy when compared with levels before intubation, and that even if levels of oral bacteria were decreased by oral and oropharyngeal irrigation, the duration of effect was only 3 hours.[11] However, topical application of tetracycline ointment to the dorsum of the tongue can reduce the number of bacteria in the oropharyngeal fluid immediately to the level of that before intubation for 6 hours in patients undergoing oral cancer surgery and intubated via trachectomy.[9]

Following on from the results of this preliminary research, we conducted a multicenter, randomized control trial (RCT) to investigate the ability of topical application of tetracycline to prevent SSI in patients undergoing oral cancer surgery.

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2. Methods

2.1. Study design

This multicenter RCT was approved by the institutional review boards at Nagasaki University Hospital and all participating hospitals and, is registered at the University hospital Medical Information Network Clinical Trials Registry (UMIN000018318), and conformed to the tenets of the Declaration of Helsinki.

The study participants were allocated to an intervention group or a control group using a stratified randomization method with adjustment according to the treating institution and whether a free flap or a pedicle flap was used. The sample size was calculated from a previous report and our pilot study.[1–9] We assumed a 30% incidence of SSI in the control group and that intervention could reduce this figure to 15%. A 2-tailed significance level of $\alpha = 0.05$ and a power of 0.90 required enrollment of 132 patients. Allowing for a dropout rate of 10%, our recruitment target was 148 patients (n = 74 in each group) over a 2-year period.

2.2. Patients

Patients with oral squamous cell carcinoma who underwent tracheotomy, neck dissection, tumor resection, and reconstructive surgery using a free or pedicle flap at 1 of 7 hospitals (Keiyukai Sapporo Hospital, Tokai University Hospital, Shinshu University Hospital, Nara Medical University Hospital, Osaka University Hospital, Okinawa Chubu Hospital, and Nagasaki University Hospital) were enrolled in the study between January 2015 and December 2016. Written informed consent was obtained from each patient. Patients in whom total necrosis developed in the flap and those who were extubated in the first 48 hours postoperatively were excluded.

2.3. Variables

The objective variable was occurrence of SSI. The following factors were identified from the medical records and investigated as predictive variables. Demographic factors (age, sex, body mass index, diabetes mellitus, Eastern Cooperative Oncology Group performance status,[12] cigarette smoking status, and alcohol consumption), laboratory data (hemoglobin, serum albumin, and serum creatinine), treatment-related factors (T stage, N stage, operating time, intraoperative blood loss, type of flap, use of a metal plate, neoadjuvant chemotherapy, preoperative radiotherapy, and history of surgery and/or radiotherapy in the oral region), and occurrence of SSI were recorded. SSI was defined according to the Centers for Disease Control and Prevention (CDC) criteria[13] at 1 month after surgery.

2.4. Intervention

All patients received routine preoperative oral care from the time the decision for hospitalization was made, which included oral health instruction, removal of dental calculus, professional mechanical tooth cleaning, and extraction of infected tooth. Patients were instructed to clean teeth by toothbrush, interdental brush, dental floss, followed by gargling 3 times per day. Edentulous patients received only cleaning of the tongue and denture, and instruction to gargling. All patients received final oral cleaning by a dental hygienist the day before surgery. Parenteral ampicillin/sulbactam was administered intraoperatively and for several days after surgery. Patients in the control group received oral care consisting of irrigation of the oral cavity with saline every 6 hours for 48 hours after surgery. Patients in the intervention group received similar oral care followed topical application of approximately 10 g of tetracycline 3% ointment on the dorsum of the tongue every 6 hours for 48 hours after surgery (Fig. 1). Tetracycline ointment was not placed directly on the flap so as to avoid interference with checking any color change in the flap.

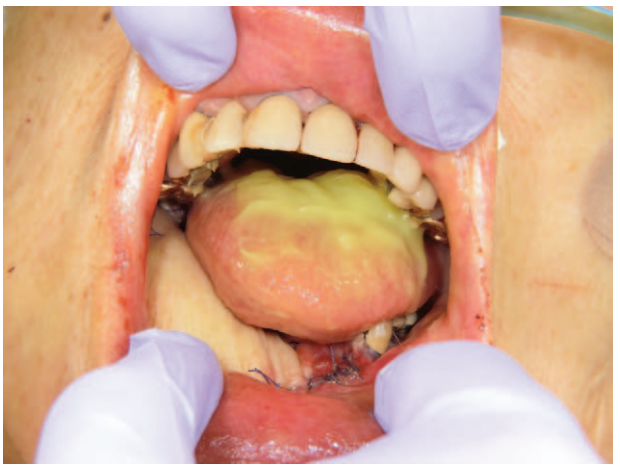

Figure 1. Topical administration of tetracycline ointment on the dorsum of the tongue.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 24.0 software (Japan IBM Corp., Tokyo, Japan). Background factors in the 2 groups were analyzed using Fisher exact test or the Mann-Whitney *U* test as appropriate. Next, the correlations between each predictive variable and occurrence of SSI were tested by stepwise multivariate logistic regression analysis.

3. Results

One hundred twenty-one patients were enrolled in the study over the 2-year recruitment period. Three patients in whom surgery was canceled and 1 patient whose flap became necrotic because of thrombosis of the anastomosed vessel were excluded, leaving 117 patients (56 in the intervention group and 61 in the control group) for analysis (Fig. 2).

The variables in each group are summarized in Table 1. Mean body mass index in the intervention group was significantly lower than that in the control group. No significant differences in the other variables were found between the 2 groups.

SSI occurred in 33 (28.2%) of the 117 patients [11/56 (19.6%) in the intervention group and 22/61 (36.1%) in the control group]. By univariate analysis, the incidence of SSI was significantly correlated with operation time (*P* value .003; Table 2). Multivariate analysis showed a significant correlation of incidence of SSI with operating time (odds ratio 1.003, 95% confidence interval 1.001–1.004) and administration of topical tetracycline (odds ratio 0.413, 95% confidence interval 0.172–0.992; Table 3). Although the number of patients enrolled in the study did not reach the target, the effect of the intervention was confirmed in multivariate analysis, so the number of patients recruited was considered to be adequate.

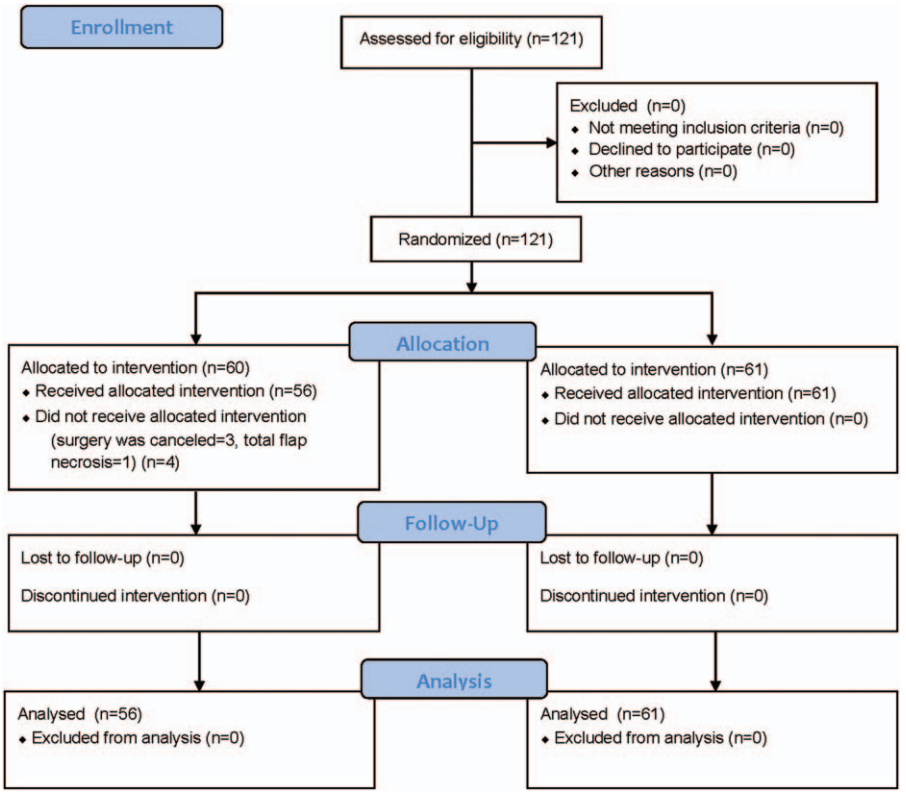

Figure 2. Flow diagram.

Table 1

Background factors of patients in the intervention and control groups.

Variable	Category	Intervention group	Control group	*P*
Age, yr		66.2 ± 12.7	65.2 ± 13.0	.680
Sex	Male	33 (45.2%)	40 (54.8%)	.567
	Female	23 (52.3%)	21 (47.7%)	
Body mass index		22.0 ± 3.50	23.2 ± 2.66	.044*
Diabetes mellitus	(−)	49 (50.0%)	49 (50.0%)	.326
	(+)	7 (36.8%)	12 (63.2%)	
Performance status	0	47 (49.0%)	49 (51.0%)	.639
	≥1	9 (42.9%)	12 (57.1%)	
Smoking status	(−)	35 (43.2%)	46 (56.8%)	.162
	(+)	21 (58.3%)	15 (41.7%)	
Alcohol consumption	(−)	39 (48.8%)	41 (51.3%)	.844
	(+)	17 (45.9%)	20 (54.1%)	
Hemoglobin, mg/dL		12.57 ± 1.88	13.25 ± 2.14	.074
Albumin, g/dL		4.02 ± 0.46	4.08 ± 0.51	.537
Creatinine, mg/dL		0.84 ± 0.21	0.89 ± 0.59	.542
T stage	T1–2	20 (51.3%)	19 (48.7%)	.695
	T3–4	36 (46.2%)	42 (53.8%)	
N stage	N0–1	33 (44.6%)	41 (55.4%)	.443
	N2–3	23 (53.5%)	20 (46.5%)	
Operating time, min		689 ± 232	686 ± 271	.954
Blood loss, g		574 ± 425	598 ± 356	.738
Type of flap	Free	53 (46.9%)	60 (53.1%)	.348
	Pedicled	3 (75.0%)	1 (25.0%)	
Use of a metal plate		33 (42.9%)	44 (57.1%)	.172
		23 (57.5%)	17 (42.5%)	
Neoadjuvant chemotherapy	47 (47.0%)	53 (53.0%)	0.794	
		9 (52.9%)	8 (47.1%)	
Preoperative radiotherapy	53 (51.8%)	57 (48.2%)	1.000	
		3 (42.9%)	4 (57.1%)	
History of surgery		48 (50.5%)	47 (49.5)%	.248
		8 (36.4%)	14 (63.6%)	
History of radiotherapy		53 (47.3%)	59 (52.7%)	.699
		3 (60.0%)	2 (40.0%)	
Total		56	61	

Values are expressed as the mean ± standard deviation or number (%).
* Significant.

Table 2

Univariate analysis between each variable and occurrence of surgical site infection.

Variable	Category	SSI (−)	SSI (+)	*P*
Age, yr		66.17 ± 12.15	64.53 ± 14.468	.532
Sex	male	50 (68.5%)	23 (31.5%)	.397
	female	34 (77.2%)	10 (22.8%)	
BMI		22.48 ± 3.23	22.95 ± 3.1	.478
Diabetes mellitus	(−)	71 (72.2%)	27 (27.8%)	.782
	(+)	13 (68.4%)	6 (31.6%)	
Performance status	0	69 (71.9%)	27 (28.1%)	1.000
	≥1	15 (71.4%)	6 (28.6%)	
Smoking habit	(−)	57 (70.3%)	24 (29.7%)	.662
	(+)	27 (75%)	9 (25%)	
Drinking habit	(−)	57 (71.3%)	23 (28.7%)	1.000
	(+)	27 (73%)	10 (27%)	
Hemoglobin, mg/dL		12.86 ± 1.92	13.09 ± 2.34	.594
Albumin, g/dL		4.06 ± 0.47	4.02 ± 0.54	.703
Creatinine, mg/dL		0.88 ± 0.52	0.83 ± 0.21	.565
T stage	T1–2	30 (76.9%)	9 (23.1%)	.514
	T3–4	54 (69.2%)	24 (30.8%)	
N stage	N0–1	52 (70.3%)	22 (29.7%)	.675
	N2–3	32 (74.4%)	11 (25.6%)	
Operation time, min		644.04 ± 241.93	798.61 ± 247.285	.003*
Blood loss, g		544.08 ± 338.43	693.56 ± 484.56	.061
Sort of flap	Free flap	80 (70.8%)	33 (29.2%)	.576
	Pedicled flap	4 (100%)	0 (0%)	
Use of metal plate	(−)	57 (74.0%)	20 (26.0%)	.518
	(+)	27 (67.5%)	13 (32.5%)	
Neoadjuvant chemotherapy	(−)	71 (71.0%)	29 (29.0%)	.776
	(+)	13 (76.5%)	4 (23.5%)	
Preoperative radiotherapy	(−)	79 (71.8%)	31 (28.2%)	1.000
	(+)	5 (71.4%)	2 (28.6%)	
History of surgery	(−)	66 (69.5%)	29 (30.5%)	.302
	(+)	18 (81.8%)	4 (18.2%)	
History of radiotherapy	(−)	80 (71.4%)	32 (28.6%)	1.000
	(+)	4 (80.0%)	1 (20.0%)	
Topical tetracycline	(−)	39 (63.9%)	22 (36.1%)	.064
	(+)	45 (80.4%)	11 (19.6%)	

Values are expressed as mean ± SD or number (%).
* Significant.
SSI = surgical site infection.

4. Discussion

SSI is one of the most frequent postoperative complications of oral cancer surgery. The risk of SSI has been reported to be 10.9% to 45.0% in patients who undergo head and neck cancer surgery, despite parenteral antibiotic prophylaxis.[1–8] SSI not only causes a prolonged hospital stay and decreased quality of life in patients who undergo oral cancer surgery, but also adversely impacts the outcome because of the need to delay postoperative treatment in patients with adverse prognostic features. The CDC guidelines[13] 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 colony-forming units per milligram, so the risk of SSI in oral cancer surgery is likely to be high.

There has been a good deal of research on the use of topical antibiotic therapy to reduce the risk of SSI in various types of clean and clean-contaminated surgical wounds. The review by Halasz[14] mentions a report from 1956 in which irrigation of the operative site with tetracycline reduced the incidence of SSI after appendectomy from 8.1% to 1.2%. The same review also mentions that by 1977 there were 11 RCTs and 6 retrospective studies supporting the clinical effectiveness of topical antibiotics in reduction of SSI. In a more recent review, Alexander et al[10] concluded that topical antibiotics are effective in reducing wound infections and may be as effective as systemic antibiotics, but that the most effective method and duration of application had not been established. They also stated that high antibiotic concentrations can be achieved by injection of an antibiotic directly into the wound and retained after closure or by implant of a sustained-release antibiotic formulation containing biodegradable materials that do not need removal, but that use of such materials in

Table 3

Multivariate analysis between each variable and occurrence of surgical site infection.

Variable	Category	*P*	OR	95% CI
Operating time, min		.004*	1.003	1.001–1.004
Topical tetracycline	(+) vs (−)	.048*	0.413	0.172–0.992

* Significant.
CI = confidence interval, OR = odds ratio.

Table 4

Clinical trial on prevention of surgical site infection of the head and neck surgery by topical antibiotics administration.

Reference	Year	Study design	Patients (n)	Inclusion criteria	Method	Result
Barton and Moir[17]	1983	Pilot study	16	Major head and neck surgery	Gentamicin beads inserted in the wound for 48 hours	Three of 16 patients developed SSI
Simons et al[19]	2001	RCT	62	Head and neck cancer surgery with flap reconstruction	Intraoperative irrigation of piperacillin/tazobactam and mouthwash immediately before surgery and once a day for 2 days postoperatively	Not significant
Shuman et al[20]	2012	RCT	84	*Staphylococcus aureus* carrier, head and neck cancer	Intranasal mupirocin and chlorhexidine skin rinse for 5 days before surgery	Not significant

RCT = randomized control trial, SSI = surgical site infection.

clinical studies had been very limited. Administration of a nonabsorbable oral antimicrobial agent in divided doses on the day before surgery is strongly recommended in the CDC guidelines for the prevention of SSI in colorectal surgery.[13] Chang et al[15] performed a meta-analysis of 15 RCTs including 6979 patients and reported that gentamicin-collagen implants significantly decreased the incidence of SSI after cardiac surgery, colorectal cancer surgery, or breast cancer surgery. In a further review of 9 RCTs involving 3396 patients, Van Rijen et al[16] reported that intranasal application of mupirocin ointment achieved a statistically significant reduction in the rate of *Staphylococcus aureus* infection, including bacteremia, exit-site infections, peritonitis, respiratory tract infections, skin infections, SSIs, and urinary tract infections, when compared with placebo or no treatment. However, they also mentioned that this effect disappeared if the analysis only included SSI, possibly due to a lack of power. Moreover, they found that the infection rate caused by microorganisms other than *S aureus* was significantly higher in patients treated with intranasal mupirocin ointment when compared with control patients,[16] so this method did not become standard prophylaxis for SSI.

As mentioned above, the ability of topical administration of antibiotics to prevent SSI has been examined in various types of surgery. Parenteral antibiotic therapy is used routinely to reduce the risk of SSI in patients undergoing major oncologic head and neck surgery. Nevertheless, the reported incidence of SSI remains relatively high, so some investigators have attempted to reduce it by topical administration of antibiotics (Table 4). Barton and Moir[17] reported that inserting gentamicin beads into major surgical wounds of the head and neck was effective for prevention of SSI; however, 3 of the 16 patients included in their pilot study developed SSI in spite of the intervention. Grandis et al[18] reported that clindamycin mouthwash was more effective than parenterally administered clindamycin in reducing oral bacteria levels. They also demonstrated that topical clindamycin prophylaxis as a preoperative mouthwash, combined with intraoperative irrigation and a postoperative mouthwash, was effective in patients undergoing laryngectomy with neck dissection. Based on these results, Simons et al[19] performed a randomized, prospective clinical trial on the efficacy of topical antibiotic prophylaxis in patients undergoing head and neck surgery with flap reconstruction. However, they concluded that additional use of topical piperacillin/tazobactam administered as a mouthwash immediately before surgery and once a day for 2 days postoperatively did not enhance the prophylactic benefit of parenteral antibiotics alone. Shuman et al[20] performed an RCT in 84 patients with head and neck cancer and carrying *S aureus* in the nasal cavity and reported that intranasal mupirocin and use of a chlorhexidine-containing skin rinse for 5 days before surgery did not decrease the incidence of SSI.

The reason for the failure of topical antibiotic prophylaxis to prevent SSI in head and neck surgery seems to lie in the antibiotic formulations used. Antibiotic mouthwashes reduce the numbers of intraoral bacteria present, but the concentration of the drug decreases immediately after use and its ability to protect against SSI diminishes over a few hours. Furthermore, topical mupirocin administered preoperatively does not prevent growth of intraoral bacteria during intubation or after surgery. We previously reported that numbers of bacteria on the dorsum of the tongue and in the oropharyngeal fluid increased rapidly after intubation despite parenteral administration of antibiotics but those on the buccal mucosa and palate did not increased, and that topical administration of tetracycline ointment showed excellent efficacy in reducing the numbers of bacteria in the oropharyngeal fluid for about 6 hours after application.[9] The concentration of tetracycline in oropharyngeal fluid was in the range of 89.3 to 183.4 mg/mL for up to 5 hours after intubation, which is at least 100-fold higher than the minimum inhibitory concentration of tetracycline for most oral bacteria. Maintenance of such a high drug concentration over an extended period was likely attributable to the loss of swallowing function during intubation.

Following on from the results of our pilot study,[9] we conducted this RCT to investigate the ability of topical antibiotic therapy to decrease the incidence of SSI in patients with oral cancer undergoing major oncologic surgery. Tetracycline was selected because it has been widely used as a topical antibiotic and has rarely induced methicillin-resistant *S aureus*. All patients received parenteral ampicillin/sulbactam. Another reason for using tetracycline was that the effects of combined use of systemic and topical antibiotics may be lessened if the same antibiotic is used.[10] The optimal duration of topical tetracycline therapy was determined to be 48 hours because the risk of SSI is highest in the 48 hours postoperatively, and longer administration may promote resistant microorganisms.

Preoperative radiotherapy or chemotherapy could reduce host general and local immunity, but did not influence the incidence of SSI. In our RCT, logistic regression analysis showed that the incidence of SSI was lower in patients who received topical tetracycline combined with parenteral antibiotics than in those who received parenteral antibiotics alone. To the best of our knowledge, this is the first RCT to demonstrate the effectiveness of topical antibiotics in preventing SSI in patients with oral cancer. We attribute our successful results to the sustained high concentrations of tetracycline that can be achieved because of the decreased swallowing function after major oncologic surgery with reconstruction and tracheotomy. Therefore, this method is

not recommended for patients undergoing minor oral cancer surgery or surgery at anatomic sites that do not affect the ability to swallow.

Our study has some limitations. First, our sample size was small. Second, we applied tetracycline ointment to the dorsum of the tongue, whereas other methods, such as an antibiotic-containing collagen sponge, may have been more effective for preventing SSI. Further experimental and clinical studies are needed to determine the most appropriate method of topical antibiotic therapy in patients undergoing major oral cancer surgery.

Our results hence indicate that administration of topical tetracycline for 48 hours postoperatively is an effective way of preventing SSI after oral cancer surgery.

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