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Original Article

Inhibitory effect of topical antibiotics/antiseptics administration on bacterial growth in the open wound of the jawbone surgery: Randomized controlled, preliminary study

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Abstract *Background/purpose:* TThe bone cavities after extirpation of cysts or tumor of the jawbone requires the insertion of gauze containing various antibiotics/antiseptics to minimize the risk of pain, bleeding, and surgical site infection (SSI). However, there have been few reports on the efficacy of topical administration of antibiotics/antiseptics to an open wound of the jawbone. To compare the inhibitory effects of topical povidone-iodine gel and tetracycline ointment on the jawbone wound bacterial growth after extirpation of cyst or tumor.
Materials and methods: This is a preliminary, randomized controlled, open-labeled trial. Eighteen patients were randomly assigned into two groups. In povidone-iodine (PI) group, gauze mixed with povidone-iodine gel was inserted into the bone cavity wound, and in tetracycline (TC) group gauze mixed with tetracycline ointment was inserted after extirpation of cyst or tumor of the jaw bone. In both groups, gauze was removed 48 h after surgery, and examined by bacterial culture and real-time polymerase chain reaction (PCR) using primers detecting total bacteria and MRSA.

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Results: The topical application of tetracycline ointment was superior to that of povidone-iodine gel concerning inhibitory effects of total bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA).
Conclusion: This preliminary study suggests that the insertion of gauze mixed with tetracycline ointment is recommended for bone wounds after extirpation of cyst or tumor of the oral cavity.

Introduction

Primary suturing is preferred in surgical wounds for its early healing and prevention of surgical site infection (SSI). When primary suturing is difficult in oral soft tissue surgery, the wound may be covered by a free mucosal graft, free skin graft, or various pedicled or free vascularized flaps, but bone cavities after extirpation of cysts or tumor of the jawbone are left open and often secondary healing is awaited. A small bone cavity such as tooth extraction can heal immediately even with an open wound, whereas a larger bone cavity requires the insertion of gauze containing antibiotics/antiseptics until the bone surface is covered by the surrounding mucous membrane to minimize the risk of pain, bleeding, and SSI.

Various antibiotics and antiseptics have been topically applied to closed or open wounds of the skin, and most studies concluded that it is not clear which of these agents works effectively for infection prevention and cure.[1–3] On the other hand, there have been few reports on the efficacy of topical administration of antibiotics/antiseptics to an open wound of the jawbone. In particular, the antiseptic povidone-iodine gel and the antibiotic tetracycline ointment have been used safely in various oral treatments including oral care, therefore; gauze containing these agents is generally inserted in an open wound of the jawbone. The purpose of the study is to compare the bacterial growth inhibitory effects of gauze containing povidone-iodine gel and tetracycline ointment on the bone cavity after extirpation of bone cyst or tumor.

Materials and methods

Study design

This is a preliminary, randomized controlled, open-labeled trial investigating the bacterial inhibitory effect of topical application of povidone-iodine gel and tetracycline ointment on the bone cavity after extirpation of a cyst or benign tumor. This study was conducted as a specific clinical study following the Clinical Research Law enacted in April 2018 in Japan. Written informed consent was obtained from each participant. This study was performed in accordance with the 2013 Declaration of Helsinki and was approved by the Clinical Research Review Board at Nagasaki University (CRB-19-008-1). This study was registered in Japan Register of Clinical Trials (jRCT) on September 3, 2019 (jRCTs071190024).

Patients

The subjects consisted of 18 patients who underwent extirpation of a cyst or benign tumor of the jawbone between September 3, 2019, and April 30, 2020, and whose wound was left open. Patients judged to be lacking cognitive ability, patients with hypersensitivity to iodine or tetracycline, and patients with diabetes mellitus or other compromised diseases were excluded.

Intervention

Patients were assigned randomly into the two groups using a computer allocation method. In povidone-iodine (PI) group, gauze mixed with 10% povidone-iodine gel (ISODINE® GEL 10%, Mundipharma K.K, Tokyo, Japan) was inserted into the bone cavity after removal of cyst or tumor, and in tetracycline (TC) group, gauze mixed with tetracycline ointment (Achromycin® ointment, Sun Pharma Japan LTD., Tokyo, Japan) was inserted. In both groups, gauze was removed 48 h after surgery. The deepest part of the inserted gauze was cut into two small pieces of 5 mm square, one was used as a sample for bacterial culture examination, and the other was used as a sample for real-time polymerase chain reaction (PCR).

Data examined

The data examined for a description of patient characteristics included age, sex, primary disease, primary site (upper jaw/lower jaw), smoking habit in the past one year, leukocyte count, lymphocyte count, hemoglobin, albumin, creatinine, C-reactive protein (CRP), symptoms of infection at surgery, and the incidence of SSI.

Estimation of the number of bacteria by real-time PCR

Genomic DNA from the inserted gauze was isolated by a DNA extraction kit (InstaGene Matrix; Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions. The concentration of total bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) was estimated based on real-time PCR data. For the standard calibration curve for quantitative real-time PCR, the DNA sequence of the target microorganism was synthesized, and artificial DNA was used as reported previously.[4] The primers used were as shown in Table 1. PCR reaction conditions are

Table 1 Primers used in the study.

Target	Gene	Sequence	Size
Total *Streptococci*	16S rRNA	TCGGATCGTAAAGCTCTGTTGTA GGACAACGCTCGGGACCTAC	137
MRSA	MecA	GCAATCGCTAAAGAACTAAG GGGACCAACATAACCTAATA	222

Abbreviations: MRSA, Methicillin resistant *Staphylococcus aureus*; RNA, Ribonucleic acid.

as previously reported.[4] After completion of amplification, fluorescence signals were detected to generate a melting curve, and the specificity of the amplified product was confirmed. Data were analyzed using Thermal Cycler Dice® Real-time System software (TaKaRa BIO Inc, Shiga, Japan). The concentration of microorganisms was the copy number estimated based on the amplification and calibration curves.

Endpoint

The primary endpoint of the study is a comparison of the number of total bacteria of the deepest part of the inserted gauze of the PI group and TC group measured by real-time PCR. The secondary endpoints are the incidence of infection symptoms at the removal of gauze and the results of bacterial culture examination.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24.0; Japan IBM Co., Ltd., Tokyo, Japan). The data of patient characteristics were analyzed utilizing descriptive and inferential statistics. The differences between total bacterial counts in the PI and TC groups were analyzed by one-way ANOVA when the data were parametric, and by Mann—Whitney U-test when the data were not parametric. Shapiro-Wilk test was used to judge the distribution of data was parametric or non-parametric.

Results

Patient characteristics

Eighteen patients were enrolled in the study and randomized to one of the two treatment sequences. No patient withdrew, and 18 patients completed the full study protocol, as shown in the CONSORT flow diagram (Fig. 1). Patient characteristics are shown in Table 2. Eight patients were males and 10 were females. The primary disease was a bone cyst in 12 patients, medication-related osteonecrosis of jaw (MRONJ) in 2, benign tumor in 2, malignant tumor in 1, and palatal torus in 1. Regarding the histopathological type, 12 cysts consisted of 6 dentigerous cysts, 4 radicular cysts, 1 odontogenic keratocyst and 1 nasopalatine duct cyst. Two benign tumors were pleomorphic adenoma and ameloblastoma. One case of malignant tumor was maxillary gingival melanoma. Povidone iodine gel was administrated in 9 patients and tetracycline ointment in 9.

Bacterial culture examination

The results of qualitative analysis by bacterial culture are shown in Table 3. Bacteria were identified in all 9 patients in the PI group, and the strains were *gram-positive cocci*, α-*Streptococcus*, *Streptococcus mitis* group, *Streptococcus anginosus* group, *Streptococcus warneri*, *Haemophilus parainfluenzae*, *H. parainfluenzae*, *Bacillus*, *Klebsiella*, *Enterobacter*, and *Pseudomonas aeruginosa*. On the other hand, bacteria were identified in 5 of 9 patients in the TC

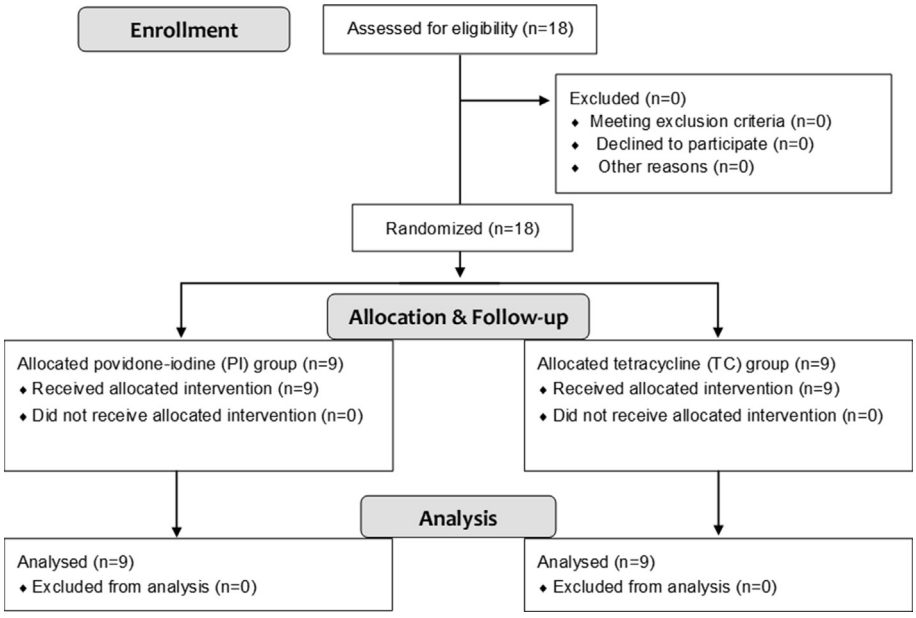

Figure 1 CONSORT flow diagram.

Table 2 Patient characteristics.

Factor		PI group	TC group	*p*-value
Age (mean; SD)	years	67.7 ± 13.9	51.9 ± 18.3	0.071
Sex	male	4	4	1.000
	female	5	5	
Site	upper jaw	4	4	1.000
	lower jaw	5	5	
Diabetes mellitus	-	7	7	1.000
	+	2	2	
Smoking habit	-	8	7	1.000
	+	1	2	
Leukocytes (mean; SD)	/μL	5031 ± 1283	7069 ± 1342	0.010*
Hemoglobin (mean; SD)	g/dL	12.7 ± 1.49	14.3 ± 1.32	0.043*
Albumin (mean; SD)	g/dL	4.03 ± 0.398	4.08 ± 0.417	0.836
Creatinine (mean; SD)	mg/dL	0.739 ± 0.153	0.737 ± 0.136	0.983
Systemic antibiotics*	AMPC	3	1	
	SBT/ABPC	4	4	
	CMZ	1	2	
	CTRX	1	0	
	PIPC/TAZ	0	1	
	CAM	0	1	
Primary disease	cyst	5	7	
	MRONJ	2	0	
	benign tumor	1	1	
	malignant tumor	0	1	
	palatal torus	1	0	
Total		9	9	

Abbreviation: AMPC, ampicillin; CAM, clarithromycin; CTRX, ceftriaxone; CMZ, cefmetazole; MRONJ, Medication-related osteonecrosis of the jaw; PI, povidone-iodine; PIPC/TAZ, piperacillin/tazobactam; SBT/ABPC; sulbactam/ampicillin; SD, Standard deviation; TC, tetracycline.
*indicates a significant difference ($P < 0.05$).

Table 3 Results of bacterial culture examination.

	PI group	TC group
Bacteria detected by culture	*α-Streptococcus* (2 patients)	*α-Streptococcus* (2 patients)
	gram positive cocci	*Streptococcus mitis group* (2 patients)
	Streptococcus mitis group (3 patients)	*Streptococcus parasanguinis*
	Streptococcus anginosus group	*Streptococcus warneri*
	Streptococcus warneri	*Streptococcus viridans*
	Haemophilus parainfluenzae	*Streptococcus sanguinis*
	Neisseria	
	Bacillus	
	Enterobacter	
	Klebsiella	
	Pseudomonas aeruginosa	

Abbreviation: PI, povidone-iodine; TC, tetracycline.

group, and all the strains were oral Streptococci such as *α-Streptococcus*, *S. mitis* group, *Streptococcus sanguinis*, *Streptococcus parasanguinis*, and *S. warneri*.

Bacterial count in the gauze of the PI and TC groups

Fig. 2 shows the number of bacteria in the PI and TC groups by real-time PCR. Total bacterial counts in the TC group were significantly lower than those in the PI group. MRSA was detected in 8 of 9 patients in the PI group, while it was detected in only 3 of 9 in the TC group. Median MRSA counts were lower in the TC group than in the PI group, but there was no statistically significant difference (Fig. 3).

Incidence of SSI

None of the enrolled patients developed SSI.

Discussion

In oral soft tissue surgery, the raw surface is covered with a mucosal graft, skin graft, pedicled or vascularized free flap, a biomaterial such as artificial dermis with collagen, or polyglycolic acid sheet.[5,6] On the other hand, intraoral surgery often leaves the wound open, such as tooth extraction.

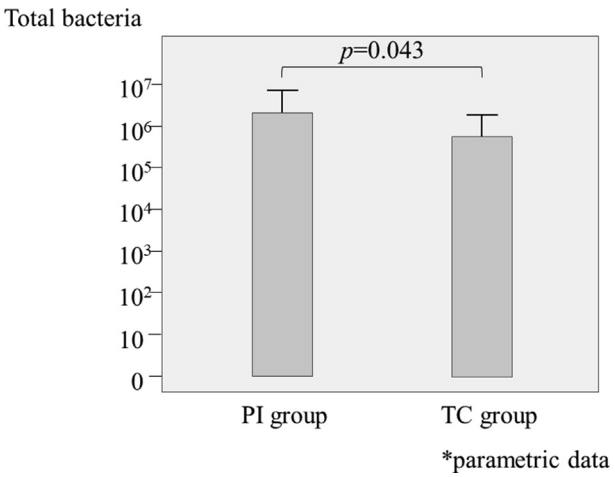

Figure 2 Total bacterial count in the gauze of the PI and TC groups. Total bacterial counts in the TC group were significantly lower than those in the PI group. PI, povidone-iodine; TC, tetracycline.

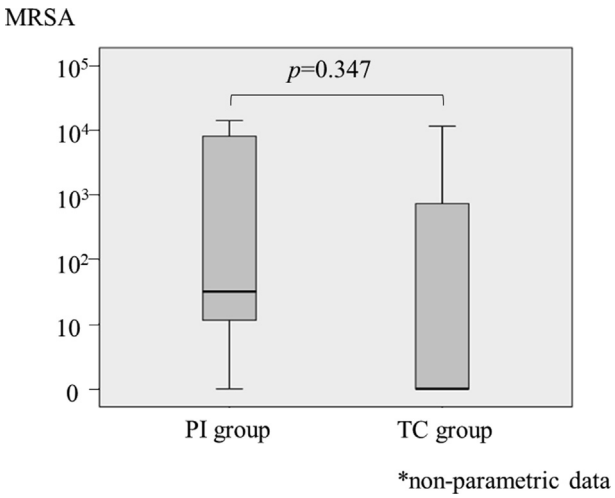

Figure 3 MRSA count in the gauze of the PI and TC groups. Median MRSA counts were lower in the TC group than in the PI group, but there was no statistically significant difference. MRSA, Methicillin resistant *Staphylococcus aureus*; PI, povidone-iodine; TC, tetracycline.

The effect of systematic antibiotics on preventing postoperative infection of tooth extraction has been controversial.[7–11] According to Cochrane Review, postoperative infection of tooth extraction occurred in 7.6% of patients; 3.4% in those receiving antibiotics, and 11.8% in those receiving placebo. The risk of infection after extracting wisdom teeth from healthy young people is about 10%; however, it may be up to 25% in patients who are already sick or have low immunity. There is evidence that prophylactic antibiotics reduce the risk of infection, dry socket, and pain following third molar extraction, but antibiotic usage have side effects. Additionally, there was no evidence that antibiotics prevent fever, swelling, or problems with restricted mouth opening in patients who have had wisdom teeth removed. Another concern, which cannot be assessed by clinical trials, is that widespread use of antibiotics by people who do not have an infection is likely to contribute to the development of bacterial resistance. This review concludes that antibiotics given to healthy people to prevent infections may cause more harm than benefit to both the individual patients and the entire population.[12] Postoperative infection after the extirpation of the cyst of the jawbone occurs more often than that after tooth extraction. Kim et al. reported that postoperative infection occurred in 21 of 81 patients undergoing extirpation of a dentigerous cyst or odontogenic keratocyst of the jaw, despite systemic administration of antibiotics.[13] These findings may suggest that topical rather than systemic administration of antibiotics should be considered when performing tooth extraction or cyst extirpation of the jawbone.

Some investigators attempted to prevent postoperative infection of soft tissue wound by topical antibiotics/antiseptics.[2,3,14] However, to the best of our knowledge, there have been no reports describing topical antibiotics/antiseptics application after jawbone surgery. In clinical practice, gauze containing antibiotics/antiseptics is often inserted into the bone cavity immediately after jawbone surgery such as cyst extirpation to prevent bleeding and infection, but it is not established which agent is suitable for this purpose. No antibiotics/antiseptics have been approved for topical administration in the jawbone cavity in Japan except for minocycline ointment used in periodontal pockets[15] and tetracycline cone inserted into the extraction socket.[16] In this study, we examined the bacterial growth inhibitory effect of povidone-iodine gel and tetracycline ointment, which are often used in daily clinical practice.

Isodine® gel (10% povidone-iodine), as it has medical insurance coverage for mucous membrane, is often used for open wounds of the jawbone. Achromycin® ointment (3% tetracycline) is indicated for secondary infections such as superficial skin infection, deep skin infection, chronic pyoderma, trauma/burn, and surgical wounds. Although it has no indication for use in mucous membranes, it has been administered topically to the jawbone wound in clinical practice. In this study, results indicate that tetracycline ointment was significantly stronger in suppressing bacterial growth after 48 h than povidone-iodine gel. No MRSA was detected in the povidone-iodine group, and tetracycline ointment seemed to be a good topical drug for the open wound of the jaw bone.

This study has some limitations. First, this is a preliminary study with a small number of cases, and it was unclear whether the results obtained could be generalized. Next, the primary endpoint was not the incidence of postoperative infection but the number of bacteria in the wound at 48 h. The reason is that when the postoperative infection is used as the primary endpoint, the number of cases required becomes large because its incidence is relatively low and various local and general factors are involved. Moreover, it was difficult to compare whether the inhibitory effects of PI and TC groups would be different with different disease types because the number of cases was small and the histopathological types were various. However, to the best of our knowledge, this is the first study comparing the effect of topical administration of povidone-iodine and tetracycline for the control of bacterial numbers in the bone wound. Based on the results of this

preliminary study, we would like to conduct a large-scale randomized controlled study with the incidence of postoperative infection as the endpoint in the future.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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