

Prevention of Oral Candidiasis After Free Flap Surgery: Role of 3% Sodium Bicarbonate Saline in Oral Care



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Purpose: Relevant reports about oral candidiasis status and prevention measures after free flap surgery for the oral and maxillofacial region are limited. The present study explored oral candidiasis status after free flap surgery and its prevention through a prospective comparative study.

Patients and Methods: One hundred four patients were randomized to a control group (n = 54) and an experimental group (n = 50). Compared with the control group, the experimental group was provided an additional 3% sodium bicarbonate saline solution for oral care after free flap surgery. The incidence of oral candidiasis was evaluated by objective examination (saliva culture and salivary pH measurement) and subjective evaluation (clinical signs of oral candidiasis) at admission and from postoperative days 1 to 14.

Results: The salivary pH values of the 2 groups were lower than the normal salivary pH, and postoperative salivary pH values were always lower than the active range of oral lysozymes in the control group. The salivary pH values of the experimental group were higher than those of the control group from postoperative days 6 to 14 ($P < .05$). The incidence of oral candidiasis was 13.0% in the control group, which was higher than that in the experimental group (2.0%; $P < .05$). In addition, advanced age, use of a free flap for the simultaneous repair of intraoral and paraoral defects, and a combination of 2 antibiotic types were risk factors for oral candidiasis.

Conclusion: Oral candidiasis was common in patients after free flap reconstruction surgery, and the use of 3% sodium bicarbonate saline solution for oral care effectively prevented it.

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With the development of microsurgical techniques and related disciplines, free flap transfer has become widely used in the reconstruction of oral and maxillofacial tissue defects.¹ Clinical observation has shown that patients are vulnerable postoperatively to oral candidiasis because of failed oral feeding and the use of antimicrobial agents. Failure to treat such infections

in a timely fashion can cause malnutrition and metabolic disorders, thus affecting a patient's quality of life; in addition, oral candidiasis can promote the development of cancer of the oral mucosal epithelium.^{2,3} Nevertheless, there is a lack of relevant reports on the development and management of oral candidiasis after free flap surgery for the oral and

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maxillofacial region. Therefore, understanding the oral candidiasis status after free flap surgery and exploring methods for its prevention are urgent for clinical practice. The present study is a prospective comparative study conducted to explore the infection status of oral candidiasis after free flap surgery and its prevention, which also would provide a basis for future clinical research.

Patients and Methods

PATIENTS

Participants were 104 patients who underwent free flap surgery at the Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology (Beijing, China) from November 2014 through February 2016. This study was approved by the hospital ethics committee (number PKUSSIRB-20146078). Patients voluntarily cooperated with the research and provided written informed consent. With the use of Excel software (Microsoft, Redmond, WA), all patients were randomly divided into an experimental group and a control group. To prevent postoperative oral candidiasis or bacterial infections, special attention was given to plaque control and oral hygiene.⁴ All patients completed oral scaling before surgery and received postoperative cefoxitin sodium injections (Sinopharm Zhijun Pharmaceutical Co, Ltd, Beijing, China) at a dose of 2 g 2 times daily in an intravenous drip for 7 to 9 days. Inclusion criteria were patients 18 to 75 years of age, patients undergoing free flap surgery and flap reconstruction to repair intraoral defects performed by a single surgical team, fasting blood glucose levels no higher than 7.8 mmol/L, and no preoperative use of antimicrobial drugs and antifungal therapy. Exclusion criteria were positivity for the human immunodeficiency virus and the presence of oral candidiasis before surgery indicated by relevant clinical signs of oral candidiasis and positivity for *Candida* species in saliva culture.⁵

METHODS

The control group received conventional oral care therapy. From postoperative day 1 until the stomach tube was removed (phase 1), oral rinses were performed 2 times daily (at approximately 10:00 AM and approximately 6:00 PM) by rinsing with 3% hydrogen peroxide 20 mL and then with 0.9% NaCl until no obvious blood and dirt was noted. Subsequently, from pulling out the stomach tube until postoperative day 14 (phase 2), patients were advised to use compound chlorhexidine gargles 3 times daily (immediately after each of 3 meals).

In the experimental group, phase 1 consisted of the conventional oral care therapy performed in the control group and an oral rinse with 3% sodium bicarbon-

ate saline 20 mL 2 times daily; in phase 2, immediately after the use of compound chlorhexidine gargles, gargling with a 3% sodium bicarbonate saline solution was performed 3 times daily. The sodium bicarbonate saline solution was prepared by weighing a 3-g tablet of sodium bicarbonate (Hunan Hansen Pharmaceutical Co, Ltd, Yiyang, Hunan, China), grinding it, dissolving it in saline 100 mL, and mixing the solution well.

EVALUATION INDEX

Evaluation included objective examination and subjective evaluation performed on the date of admission and on postoperative days 1 to 14, respectively. Saliva culture and clinical inspection for signs of fungal infection were performed on postoperative days 8 and 14, and salivary pH was measured daily from postoperative days 1 to 14. All examinations were performed at 2 hours after breakfast (approximately 9:00 to 9:30 AM).

For objective examination, data on patients' general health and well-being, saliva culture, and salivary pH values were collected.

Saliva Culture

A 0.5-mL static saliva sample was collected and inoculated in Sabouraud medium and then thermostatically cultured at 37°C for 48 hours. The result was judged positive if colony growth was observed; subsequently, the specific bacteria were identified using CHROMagar Candida (Paris, France), counted, and quantified (based on the different types of bacteria identified).

Salivary pH Measurement

Patients were requested to gargle with water before the measurement; a precise pH indicator paper (Shang Hai SSS Reagent Co, Ltd, Shanghai, China) was gently placed at the submandibular gland orifice for 5 seconds and 2 team members observed and recorded the color changes observed in the pH paper.

Subjective evaluation was performed by 2 members who separately observed and confirmed the presence or absence of clinical signs of oral candidiasis in the oral cavity and scored the patients according to the World Health Organization relevant standards⁶: 0, no damage to the oral mucosa; 1, a single lesion smaller than 0.5 cm² in the oral mucosa; 2, patchy damage of an area of 0.5 to 1 cm² in the oral mucosa; and 3, diffuse damage larger than 1 cm² in the oral mucosa.

STATISTICAL ANALYSIS

SPSS 17.0 (SPSS, Inc, Chicago, IL) was used for data analysis. The χ^2 test was used for data enumeration, the independent-sample *t* test was used for measurement data, and the rank-sum test was used for ranked data. *P* values less than .05 were considered statistically significant.

Results

BASIC INFORMATION

In total, 139 patients were enrolled in this study. However, 35 patients were excluded (23 cases had oral candidiasis detected preoperatively, 3 cases had preoperative blood glucose levels >7.8 mmol/L, and 9 cases in whom free flap surgery was not performed owing to a scheme adjustment); therefore, 104 patients were investigated and completed the study: 54 in the control group (35 men and 19 women) and 50 in the experimental group (28 men and 22 women). No statistically significant differences in gender were observed ($\chi^2 = 0.336, P > .05$) between the 2 groups, or in age, days of antibiotic use, and days of hospitalization (Table 1).

SALIVARY PH VALUE

The *t* test was used to compare salivary pH values between the 2 groups. The average postoperative salivary pH was 6.17 (range, 6.12 to 6.26) in the control group and 6.52 (range, 6.39 to 6.62) in the experimental group. Thus, salivary pH values were significantly higher in the experimental group than in the control group from postoperative days 6 to 14 ($P < .05$; Table 2).

The average salivary pH values were plotted (Fig 1). The 2 groups exhibited salivary pH values that were lower than normal levels of salivary pH (6.7⁷). Oral lysozymes exert primarily antimicrobial effects by destroying the glycosidic bonds in the cell walls of bacteria and fungi, which is highest when the salivary pH range is 6.3 to 7.0⁸; in this study, the postoperative salivary pH was always lower than the active range of lysozymes in the control group but always within the active range in the experimental group.

SALIVA CULTURE AND CLINICAL EXAMINATION RESULTS

The χ^2 test was used to compare saliva culture results between groups (Table 3). A statistically significant difference was noted between the detection rate of *Candida* species in the oral cavity on postoper-

ative days 8 and 14 in the control group (day 8, 22.2%; day 14, 27.8%) and the experimental group (days 8 and 14, 4.0%; $P < .05$). Thirty-one samples exhibited positive saliva culture results in the 2 groups; further evaluation of bacteria classification and counts of these specimens disclosed 29 cases of *Candida albicans*, 1 case of *Candida glabrata*, and 1 case of *Candida krusei*.

The rank-sum test was used to compare clinical signs of candidiasis between the 2 groups (Table 4). According to the diagnostic criteria of oral candidiasis⁵ (relevant clinical signs of oral candidiasis and positivity for *Candida* species in saliva culture) and the results presented in Tables 2 and 4, the incidence of oral candidiasis on postoperative day 8 was 9.3% in the control group and 0% in the experimental group ($P < .05$). The incidence of oral candidiasis on postoperative day 14 was 13.0% in the control group and 2.0% in the experimental group ($P < .05$; Fig 2).

COMPARISON BETWEEN PATIENTS WITH CANDIDIASIS AND NONINFECTED PATIENTS

Age comparisons were made among the 8 candidiasis cases detected on postoperative day 14 (1 case in the experimental group and 7 cases in the control group) and the noninfected patients (Table 5).

As presented in Table 5, infected patients were older than noninfected patients ($P < .05$), which indicates age as a risk factor for oral candidiasis after free flap surgery.

Of the infected patients, 2 had maxillofacial tissue defects, for which free flap surgery was performed to simultaneously repair intraoral and paraoral defects, and 2 had bacterial infection after surgery (1 wound infection and 1 pulmonary infection); bacterial smear results showed that these cases were gram-positive cocci, and the patients were treated with cefoperazone sulbactam sodium injections (Pfizer, New York, NY) administered intravenously (1.5 g every 12 hours) for 4 days, starting from postoperative days 4 and 5, respectively. Conversely, none of these complications were observed in the noninfected patients. Thus, these findings suggest that simultaneous free flap repair of intraoral and paraoral defects and

Table 1. BASIC INFORMATION OF THE 2 GROUPS

Items	Control Group (n = 54)	Experimental Group (n = 50)	<i>t</i> Value	<i>P</i> Value
Age (yr)	51.04 ± 12.82	53.12 ± 13.25	-0.814	.418
Antibiotic use (days)	7.94 ± 1.30	7.96 ± 1.56	-0.055	.956
Hospitalization (days)	14.63 ± 3.99	15.10 ± 2.59	-0.707	.481

Note: Data are presented as mean ± standard deviation.

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Table 2. COMPARISON OF SALIVARY PH VALUE AT DIFFERENT TIME POINTS BETWEEN GROUPS

Time	Control Group (n = 54)	Experimental Group (n = 50)	t Value	P Value
On admission	6.40 ± 0.96	6.46 ± 0.75	0.374	.709
Postoperative day 1	6.26 ± 0.63	6.45 ± 0.79	1.356	.177
Postoperative day 2	6.19 ± 0.79	6.47 ± 0.78	1.823	.072
Postoperative day 3	6.13 ± 0.68	6.39 ± 0.82	1.774	.081
Postoperative day 4	6.12 ± 0.76	6.40 ± 0.81	1.821	.072
Postoperative day 5	6.12 ± 0.86	6.41 ± 0.73	1.849	.068
Postoperative day 6	6.15 ± 0.50	6.58 ± 0.53	4.256	.000*
Postoperative day 7	6.17 ± 0.37	6.62 ± 0.53	5.053	.000*
Postoperative day 8	6.15 ± 0.53	6.61 ± 0.54	4.375	.000*
Postoperative day 9	6.17 ± 0.53	6.58 ± 0.81	3.079	.003*
Postoperative day 10	6.18 ± 0.23	6.56 ± 0.26	7.910	.000*
Postoperative day 11	6.17 ± 0.37	6.57 ± 0.32	5.882	.000*
Postoperative day 12	6.18 ± 0.46	6.54 ± 0.48	3.914	.000*
Postoperative day 13	6.17 ± 0.43	6.55 ± 0.47	4.307	.000*
Postoperative day 14	6.16 ± 0.26	6.53 ± 0.49	4.864	.000*

Note: Data are presented as mean ± standard deviation.

* Statistically significant.

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a combination of 2 antibiotic types are risk factors for oral candidiasis.

Discussion

Candida species is an opportunistic pathogen and can be normally found on the skin and mucous membranes. The detection rate of oral *Candida* species in the normal adult is approximately 3 to 48%. (The difference of detection rate is related mainly to the sampling method. The detection rate of saliva culture is generally 17.18%.^{5,8,9}) Opportunistic oral candidiasis can occur in conditions that compromise immunity. Based on the available literature, the average

incidence of oral candidiasis is 8.15% in healthy individuals⁸ and 7.5 to 14.1% in patients with malignant tumors.^{10,11}

In the present study, the detection rate of *Candida* species in the oral cavity was 27.8% after free flap surgery, and the incidence of candidiasis was 13.0%, which was higher than that observed in healthy individuals and patients with malignant tumors. This high incidence of oral candidiasis after surgery can be explained as follows. First, surgery can damage the integrity of the oral mucosa, thereby jeopardizing its function as a natural physical barrier; this could be advantageous for ectopic transfer and colonization of normal micro-organisms.^{8,12} Second, postoperative

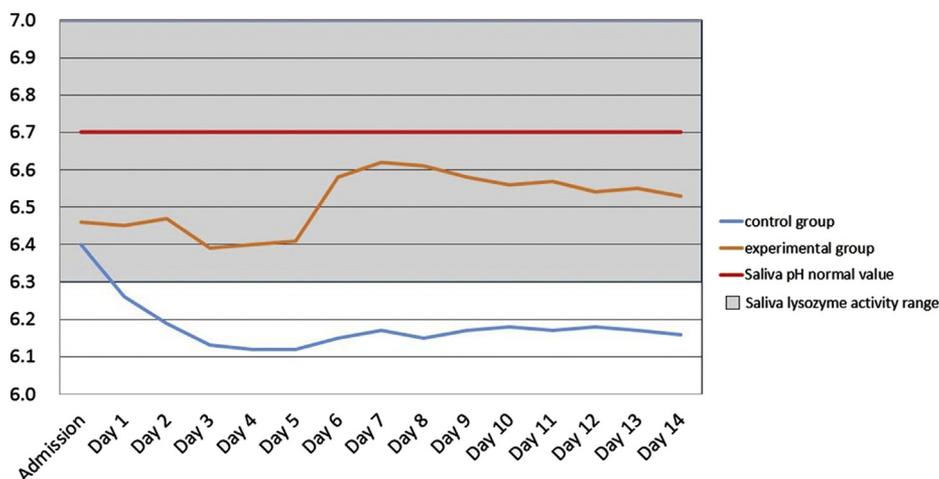


FIGURE 1. Graph shows comparison of salivary pH values at different time points between the 2 study groups.

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Table 3. COMPARISON OF SALIVA CULTURE AT DIFFERENT TIME POINTS BETWEEN GROUPS

Time	Control Group (n = 54)		Experimental Group (n = 50)		χ^2 Value	P Value
	Negative	Positive	Negative	Positive		
On admission	54	0	50	0	—	—
Postoperative day 8	42	12	48	2	7.400	.007*
Postoperative day 14	39	15	48	2	10.734	.001*

* Statistically significant.

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administration of antibacterial drugs can inhibit bacterial growth and easily cause oral dys-bacteriosis, which can trigger opportunistic fungal infections.^{8,13} Moreover, previous studies have reported that the use of at least 2 antimicrobial agents is more likely to cause dys-bacteriosis and that the incidence of fungal infections increases after the use of antimicrobials against gram-positive bacteria.⁹ These reports corroborate the findings from the present study because candidiasis was reported in 2 patients after the use of cefoperazone sulbactam sodium injections. Third, owing to failure of postoperative oral feeding in patients, micro-organisms propagate in the oral cavity, leading to the accumulation of acidic products, which decreases the oral pH^{7,12}; the activity of oral lysozymes is weakened when pH is decreased (range, 6.3 to 7.0),⁸ and this continuous (weak) acidic environment is conducive to the reproduction of acid-resistant *C albicans*.^{7,12} In this study, postoperative salivary pH in the control group was lower than that observed in healthy individuals and the active range of lysozymes, suggesting that decreased salivary pH can cause oral candidiasis. In addition, failure of oral feeding weakens the stimulation of salivary glands through the lack of mastication; thus, salivary secretion is decreased,^{8,12} and this is beneficial for the colonization of *Candida* species in the oral cavity leading to an infection. Fourth, 77.2% of patients who underwent oral and maxillofacial free

flap surgery had malignant tumors,¹ and tumor cell invasion suppresses the immunity of such patients.¹³ Fifth, the immune status and reaction to infection are weakened in the elderly, so older patients would be more prone to oral candidiasis.¹³ The present findings were consistent with these reports.

Prevention of oral candidiasis is superior to the frequent use of antifungals, which can lead to the development of drug resistance.¹⁴ According to previous studies, prevention of oral candidiasis includes 1) oral fluconazole (its primary adverse reactions are gastrointestinal reaction and liver function damage^{4,15,16}), 2) local external use of nystatin (it has limited drug absorption and clinical effects because it stimulates saliva secretion, which in turn results in its rapid dilution and clearance⁴), and 3) sodium bicarbonate in combination with physiologic saline used for plaque flushing.^{14,17} There is a lack of relevant reports on the single application of sodium bicarbonate to prevent oral candidiasis.

Intraoral pH can be adjusted through the salivary pellicle and is usually maintained at 5.6 to 8.0 (average, 6.7), primarily by the carbonate and phosphate buffer system.⁷ Lower salivary pH promotes the reproduction of *Candida* species. The utility of 3% sodium bicarbonate solution for the prevention of oral candidiasis can be explained as follows. The pH of 3% sodium bicarbonate solution ranges from 7.5 to 8.3, it adjusts the pH of the oral cavity, it dissolves mucins, and it

Table 4. COMPARISON OF CLINICAL SIGNS OF CANDIDIASIS AT DIFFERENT TIMES BETWEEN STUDY GROUPS

Time	Control Group (n = 54)				Experimental Group (n = 50)				Z Value	P Value
	0 Point	1 Point	2 Points	3 Points	0 Point	1 Point	2 Points	3 Points		
On admission	54	0	0	0	50	0	0	0	—	—
Postoperative day 8	49	3	2	0	50	0	0	0	-2.194	.028*
Postoperative day 14	47	4	3	0	49	1	0	0	-2.106	.035*

* Statistically significant.

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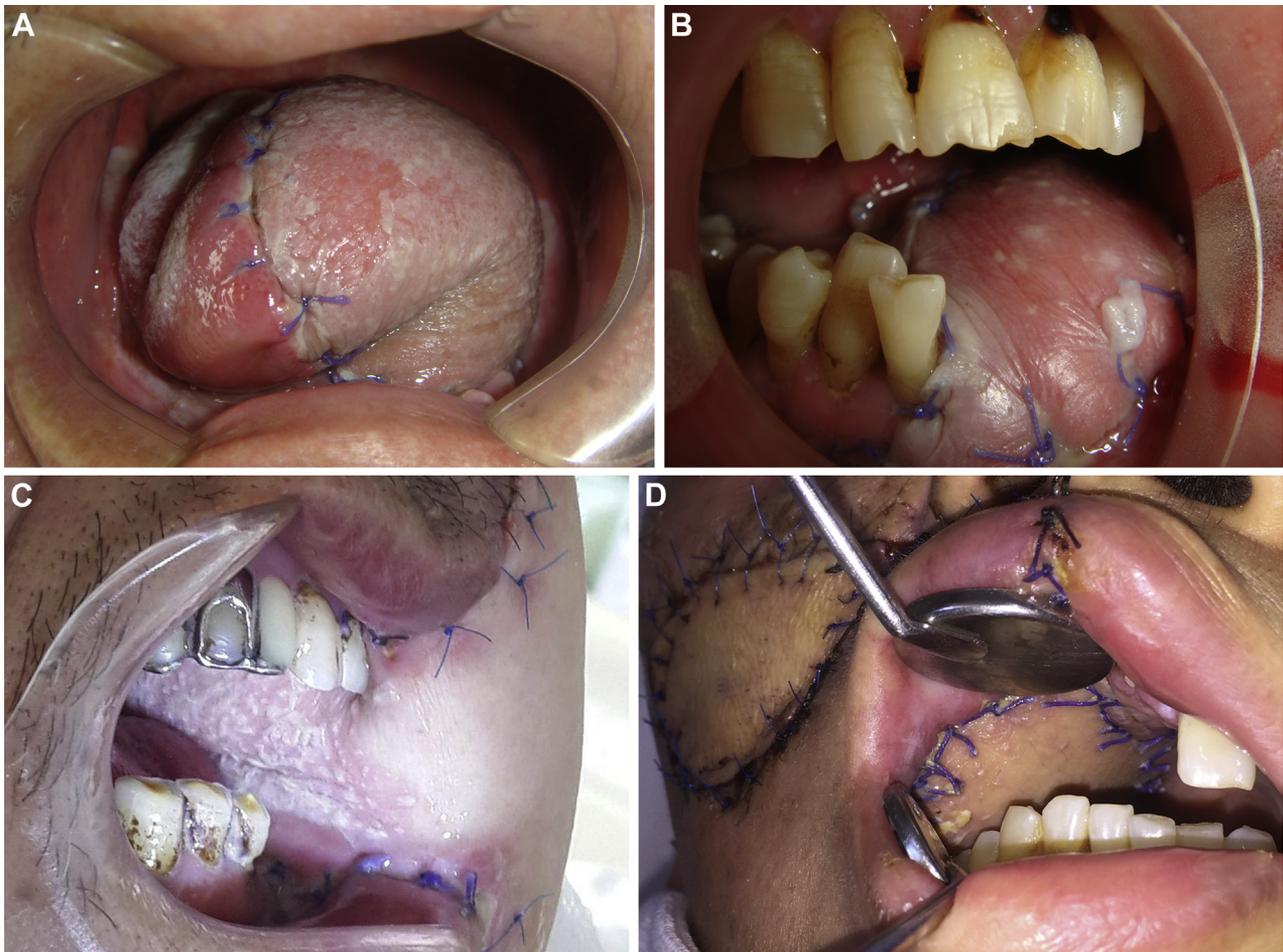


FIGURE 2. Images of patients with oral candidiasis after free flap surgery. *A*, Postoperative day 7 after using a radial forearm flap for tongue defect reconstruction. *B*, Postoperative day 7 after using a fibular flap for mandibular reconstruction. *C*, Postoperative day 8 after using an anterior lateral thigh flap for buccal defect reconstruction. *D*, Postoperative day 9 after using an anterior lateral thigh flap for reconstruction of through-and-through maxillary defects.

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destroys the acidic environment that promotes *C albicans* growth.^{18,19} Moreover, it increases the salivary flow rate and decreases the colonization of oral *C albicans*.¹⁷ Furthermore, at a concentration of 3%, sodium bicarbonate saline provides minor stimulation to the oral mucosa, with no adverse reactions such as

nausea and vomiting.¹⁹ It has been used to prevent oral mucositis in patients undergoing chemotherapy and for denture cleansing because of its low price and simple and easy gargling method.¹⁸⁻²⁰ In the present study, the average postoperative salivary pH was 6.17 in the control group and 6.52 in the experimental group. In contrast to the control group, salivary pH values in the experimental group were always within the active range of oral lysozymes, which indicates that the use of 3% sodium bicarbonate saline solution can effectively alter the salivary pH values and still maintain the activity of oral lysozymes. Moreover, the oral candidiasis infection rate was substantially lower in the experimental group than in the control group; this suggests that the use of 3% sodium bicarbonate saline for oral care can effectively prevent oral candidiasis in such patients.

In this study, salivary pH was measured 2 hours after breakfast (approximately 9:00 to 9:30 AM). Patients who underwent free flap surgery retained the stomach

Table 5. AGE COMPARISONS BETWEEN PATIENTS WITH ORAL CANDIDIASIS AND NONINFECTED PATIENTS

	n	Mean ± SD	t Value	P Value
Infected patients	8	60.29 ± 11.83	-2.573	.012*
Noninfected patients	96	51.14 ± 13.69		

Abbreviation: SD, standard deviation.

* Statistically significant.

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tube for 6 to 8 days after surgery. During the period when the stomach tube was retained, nurses provided 2 oral rinses to patients every day (approximately 10:00 AM and approximately 6:00 PM), so the salivary pH measured during this period was before the oral rinse in the morning, which was approximately 15 hours from the previous oral rinse. After the stomach tube was removed, patients were requested to gargle immediately after every meal, and their salivary pH was measured within 2 hours from the previous gargle. Based on the study results, statistically relevant differences were observed between groups for salivary pH values from postoperative day 6, which overlaps with the time when the stomach tube was removed; this suggests that sodium bicarbonate can rapidly alter salivary pH, but that its effects might weaken over time. Nevertheless, further research is required to explore whether alteration of salivary pH values can be effectively improved by increasing the frequency of sodium bicarbonate rinses.

In the experimental group, 1 patient developed candidiasis and showed improvements after subsequent treatment with fluconazole; this suggests that 3% sodium bicarbonate solution alone can be used as preventive therapy, and patients using it should be regularly examined by medical personnel. If patients present with oral mucosal hyperemia, edema or bleeding, pain in the oral mucosa, dry mouth, or gustatory differences, then clinicians must evaluate the presence of candidiasis and actively treat it.

Patients undergoing free flap surgery are at a risk of developing oral candidiasis after surgery. Advanced age, simultaneous free flap repair of intraoral and paraoral defects, and a combination of 2 antibiotic types are risk factors for oral candidiasis. Therefore, such patients must be closely followed. The use of 3% sodium bicarbonate saline for oral care can effectively prevent oral candidiasis and can be used as an effective supplement for existing oral care measures after free flap surgery.

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