Effect of perioperative oral management on postoperative complications of heart valve surgery

Toshihiro Motoi

Department of Preventive Dentistry, Kagoshima University

Graduate School of Medical and Dental Sciences

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Contents

Original paper

This thesis is based on the following original publications.

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Motoi T, Matsumoto K, Imoto Y, and Oho T., *Effect of perioperative oral management on postoperative bloodstream infection in heart valve surgery patients.* Oral Diseases, in press.

Abbreviations

AUC	Area under the curve
BSI	Bloodstream infection
IE	Infective endocarditis
IPTW	Propensity score inverse probability of treatment weighting
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PBSI	Postoperative bloodstream infection
POM	Perioperative oral management
PP	Postoperative pneumonia
PS	Propensity score
ROC	Receiver operating characteristic

Abstract

Epidemiological evidence regarding perioperative oral management (POM) for cancer surgery has been accumulated, but this evidence is not sufficient for cardiac surgery. There is a well-known relationship between oral hygiene and infective endocarditis. The effect of POM on the prevention of postoperative complications remains unclear in cardiac surgery. In this study, exploratory factor analysis was performed to examine whether a lack of POM was associated with postoperative complications of heart valve surgery. In addition, we investigated whether POM can prevent postoperative complications in patients undergoing heart valve surgery.

First, using the medical records of Kagoshima University Hospital, we retrospectively enrolled 365 patients who underwent heart valve surgery between April 1, 2010, and March 31, 2019. We extracted data on patient characteristics and set postoperative pneumonia (PP) and postoperative bloodstream infection (PBSI) as outcomes. A logistic regression analysis was performed to examine the effect of factors on the incidence of postoperative complications. Next, we retrospectively enrolled 301 patients, excluding 64 patients who underwent emergency surgery. Subjects were divided into two groups (POM group and control group) and the background was adjusted by the propensity score (PS). We then analyzed the impact of POM on PBSI, PP, and mortality

using PS inverse probability of treatment weighting (IPTW).

Significant risk factors for PP included dialysis, long operative time, and long-term intubation. Similarly, risk factors for PBSI were long-term intubation and lack of POM. Subsequently, we identified the risk factors for long-term intubation, which were common to both complications, and found they were emergency status, combined valvular disease, long operative time, and lack of POM. Regarding the effect of POM on the prevention of postoperative complications, IPTW revealed that the POM group had a lower incidence of PBSI than the control group, with an odds ratio of 0.316 ($P = 0.003$). The mortality in the POM group was significantly lower than that in the control group ($P = 0.023$).

We demonstrated that a lack of POM could be a risk factor for PBSI and long-term intubation in heart valve surgery. In addition, POM was significantly associated with decreased incidence of PBSI and mortality. These results suggest that POM is beneficial for the prevention of postoperative complications in patients undergoing heart valve surgery.

Introduction

Preoperative evaluation and treatment are necessary to quantitatively analyze and reduce the risk of complications during and after cardiac surgery. Many studies have investigated the clinical factors affecting mortality and complications after cardiac surgery [1-5]. In these reports, perioperative oral management (POM) was not included as a clinical factor, although the association between oral condition and postoperative complications has been reported. This approach of POM involves the education and practice of proper oral management by dental professionals before and after medical treatment. The purpose of POM is to prevent and reduce complications during medical treatment and improve the quality of life of patients, including those undergoing cancer and cardiovascular surgery, cancer chemotherapy, cancer radiation therapy, transplant surgery and palliative therapy. Epidemiological evidence of POM for various cancer surgeries has been accumulating. Previous research has demonstrated that POM for cancer surgery significantly suppresses postoperative pneumonia (PP) [6-9], mortality within 30 days of surgery [6], surgical site infection [8, 10], length of hospital stay [6] and medical costs [7].

In cardiac surgery, bloodstream infection (BSI), a common adverse event induced by the surgery, sometimes causes infective endocarditis (IE), which is a fatal complication.

There is a well-known relationship between oral hygiene and IE. It has been reported that IE is caused by bacteremia occurring during dental treatment [11]. The incidence of bacteremia associated with dental treatment is almost 100% for tooth extraction and is high even for dental scaling [12]. Bacteremia occurs not only during dental treatment but also during mastication and tooth brushing in daily life [13, 14]. Therefore, preoperative dental screening is recommended for patients undergoing cardiovascular surgery to ensure that any oral infection is diagnosed and definitively treated [15].

Meanwhile, the effect of POM in cardiovascular surgery has not been fully investigated. In a single-arm study, POM for cardiac surgery caused reductions in PP incidence [16] and post operative inflammation marker levels [17]. However, these studies did not investigate whether a lack of POM is a risk factor for postoperative complications of cardiac surgery.

In the present study, we extracted clinical risk factors and performed an exploratory factor analysis to examine whether a lack of POM is associated with postoperative complications of heart valve surgery. Regarding the effect of POM on the prevention of postoperative complications, the relationship between oral condition and postoperative BSI (PBSI), postoperative pneumonia (PP), and early mortality after surgery has not yet been clarified. Therefore, we next investigated whether POM prevents postoperative complications including PBSI, PP, and mortality in patients undergoing heart valve surgery.

Chapter 1

Perioperative oral management prevents complications of heart valve surgery

Subjects and Methods

1. Subjects

The present study was a single-center, retrospective, and observational study. The medical records of 365 adult patients who underwent heart valve surgery at Kagoshima University Hospital between April 1, 2010, and March 31, 2019, were enrolled in this study. Inclusion criteria are adults 20 years of age or older and undergoing open heart surgery for valvular heart disease. No exclusion criteria were set. The study protocol was approved by the ethics committee of the Kagoshima University Graduate School of Medical and Dental Sciences (number: 190057).

2. Perioperative Oral Management

Of the 365 patients, POM was performed on 180 patients who agreed to receive it. Antibiotic prophylaxis with two grams of amoxicillin capsules was administered to the patients one hour prior to the dental appointment by the prevention of bacteremia caused by dental treatment (e.g., tooth extractions, caries treatment, infected root canal treatment, dental scaling) [18]. Before surgery, dentists performed periodontal and X-ray examinations to examine the patients' oral condition. The dentists evaluated the severity of dental caries from the x-ray examination. If necessary, teeth suspected to be a source of infection (e.g. chronic apical periodontitis, fractured teeth, residual teeth roots, highly mobile teeth) were extracted, and mobile teeth were fixed to prevent them from falling out during intubation. Dental hygienists gave oral hygiene instructions to the patients, removed dental plaque using a tooth brush and adjunctive aids including interdental brush and uni-tuft brush, and eliminated dental calculus using an ultrasonic scaler. After the surgery, bedside oral examination and oral care were performed to maintain oral hygiene. Dental professionals used a tooth brush to remove plaque and a sponge brush to remove oral secretions. In intensive care unit, they provided oral care under suction to avoid aspiration. Thus, they improved the oral hygiene in group POM patients. In contrast, the remaining patients who disagreed to receive POM received no dental examination, treatment, or oral hygiene prophylaxis. All patients received routine oral care by nurses. The nurses suctioned the oral secretions and just wiped the oral cavity with gauze or a sponge brush. The significant difference between routine oral care provided by nurses and POM performed by dental professionals is whether or not meticulous dental plaque removal is performed. Dental professionals have a full understanding of the oral cavity, including configuration of each tooth and dental arcs, so they can meticulously remove dental plaque using a tooth brush and adjunctive aids. However, nurses have a limited understanding of the oral cavity and dental cleaning tools, so they can just wipe the oral cavity with gauze or a sponge brush. After discharge from the hospital, oral health care was continued in our department or the patient's family dental clinic (Fig. 1).

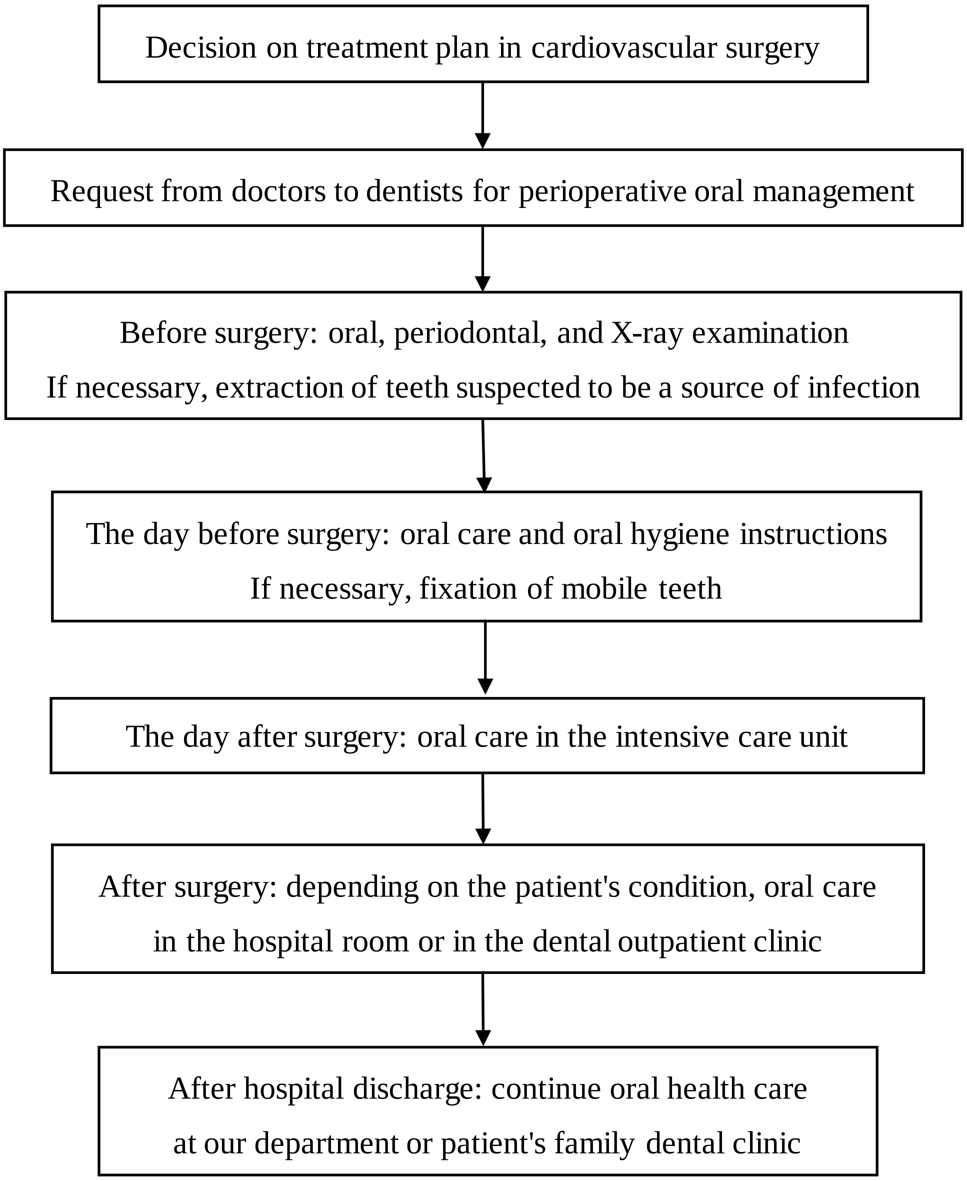

Fig. 1 Flowchart showing the timeline of POM in relation to heart valve surgery

3. Outcomes

Outcomes were set for incidence of PP and PBSI. PP was diagnosed according to the following standard criteria: fever (body temperature of ≥ 37.5°C), high C-reactive protein levels, and an infiltration shadow on chest computed tomography [19]. PBSI is infectious disease defined by the presence of viable bacterial or fungal microorganisms in the bloodstream that elicit or have elicited an inflammatory response characterized by the alteration of clinical, laboratory and hemodynamic parameters. When PBSI was suspected, arterial and venous blood samples were collected from patients and examined to identify microbial species using a culture method followed by matrix assisted laser desorption/ionization-time of flight mass spectrometry. In this study, PBSI was defined as positivity of one or more blood cultures.

4. Variables

Clinical risk factors were extracted from medical records according to previous studies [4, 5, 20]. All continuous variables were replaced with binary categorical variables, which made all the variables categorical. Age (> 65), sex, body surface area (> 1.8 m^2), New York Heart Association (NYHA) class IV, reduced left ventricular ejection fraction (LVEF) (< 50%), emergency status, combined valve disease, concomitant coronary artery bypass grafting, past cardiac surgery experience, IE, hypertension, diabetes, dialysis, long operative time (> 5 hours), long-term intubation (> 48 hours), and lack of POM were extracted. Emergency status indicated that emergency surgery was performed. Hypertension was defined as use of anti-hypertensive medication before admission or confirmed blood pressure ≥ 140/90 mmHg. Diabetes mellitus was defined as a hemoglobin A1c level ≥ 6.5%, fasting blood glucose level ≥ 126 mg/dl, or use of anti-diabetes medication. There was no data loss for any of these factors.

5. Data Analysis

The statistical method was a multivariate analysis model. First, we performed a univariate analysis with the χ^2-test or Fisher's exact test. Factors with a statistical significance level of 5% or less were extracted, and stepwise multivariate logistic regression analysis was performed. Finally, receiver operating characteristic (ROC) analysis was performed to evaluate the model. We used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for statistical analysis, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [21]. The statistical significance level was set at 5%.

Results

1. Patient's demographics and clinical characteristics

Table 1 shows patient demographics and clinical characteristics between the group who agreed to receive POM and the groups who refused. Significant differences were observed in emergency status and hypertension between two groups.

Table 1. Patient demographics and clinical characteristics

Factors	POM (+) group (n = 180)	POM (-) group (n = 185)	*P*
Age (> 65)	113 (62.8)	125 (67.6)	0.380
Sex (male)	92 (51.1)	98 (53.0)	0.754
Body Surface Area (> 1.8 m^2)	30 (16.7)	20 (10.8)	0.128
NYHA class IV	28 (15.6)	37 (20.0)	0.277
Reduced LVEF (< 50%)	36 (20.0)	52 (28.1)	0.086
Emergency status	23 (12.8)	41 (22.2)	0.020
Combined valvular disease	66 (36.7)	57 (30.8)	0.268
Concomitant coronary artery bypass grafting	37 (20.6)	43 (23.2)	0.613
Past cardiac surgery experience	30 (16.7)	28 (15.1)	0.775
Infective endocarditis	23 (12.8)	19 (10.3)	0.513
Hypertension	130 (72.2)	105 (56.8)	0.002
Diabetes	15 (8.3)	25 (13.5)	0.132
Dialysis	21 (11.7)	32 (17.3)	0.139
Long operative time (> 5 hours)	93 (51.7)	100 (54.1)	0.676

Values mean n (%).

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association functional classification.

2. Factors associated with complications incidence

The results of univariate analysis to identify the associated factors with PP and PBSI incidence are shown in Table 2.

Table 2. Univariate analysis of factors associated with PP and PBSI

Factors	Number (%)		*P*	Number (%)		*P*
	PP (-)	PP (+)		PBSI (-)	PBSI (+)	
Age (> 65)	210 (64.6)	28 (70.0)	0.599	219 (64.4)	19 (76.0)	0.283
Sex (male)	169 (52.0)	21 (52.5)	1.000	180 (52.9)	10 (40.0)	0.222
Body Surface Area (> 1.8 m^2)	45 (13.8)	5 (12.5)	1.000	48 (14.1)	2 (8.0)	0.552
NYHA class IV	54 (16.6)	11 (27.5)	0.122	59 (17.4)	6 (24.0)	0.417
Reduced LVEF (< 50%)	71 (21.8)	17 (42.5)	0.006	82 (24.1)	6 (24.0)	1.000
Emergency status	51 (15.7)	13 (32.5)	0.014	53 (15.6)	11 (44.0)	0.001
Combined valvular disease	110 (33.8)	13 (32.5)	1.000	114 (33.5)	9 (36.0)	0.828
Concomitant coronary artery bypass grafting	65 (20.0)	15 (37.5)	0.015	75 (22.1)	5 (20.0)	1.000
Past cardiac surgery experience	47 (17.2)	7 (18.9)	0.817	50 (17.2)	4 (20.0)	0.760
IE	38 (11.7)	4 (10.0)	1.000	37 (10.9)	5 (20.0)	0.188
Hypertension	206 (63.4)	29 (72.5)	0.297	221 (65.0)	14 (56.0)	0.391
Diabetes	32 (9.8)	8 (20.0)	0.062	35 (10.3)	5 (20.0)	0.174
Dialysis	39 (12.0)	14 (35.0)	< 0.001	48 (14.1)	5 (20.0)	0.385
Long operative time (> 5 hours)	160 (49.2)	33 (82.5)	< 0.001	174 (51.2)	19 (76.0)	0.021
Long-term intubation (> 48 hours)	40 (12.3)	24 (60.0)	< 0.001	45 (13.2)	19 (76.0)	< 0.001
Lack of POM	158 (48.6)	27 (67.5)	0.029	164 (48.2)	21 (84.0)	0.001

Overall, 40 patients (11.0%) had PP, and 25 patients (6.8%) had PBSI. Factors associated with PP incidence were reduced LVEF, emergency status, concomitant coronary artery bypass grafting, dialysis, long operative time, long-term intubation, and lack of POM. For PBSI incidence, the associated factors were emergency status, long operative time, long-term intubation, and lack of POM. The results of logistic regression analysis using these factors are shown in Tables 3 and 4. Factors including dialysis, long operative time and long-term intubation were significantly associated with PP incidence. Furthermore, factors including long-term intubation and lack of POM were significantly associated with PBSI incidence. ROC analysis indicated that the area under the curve (AUC) was 0.819 (95% confidence interval; 0.744-0.894) for PP incidence, and 0.887 (95% confidence interval; 0.822-0.951) for PBSI incidence.

Table 3. Logistic regression analysis of factors associated with PP

Factors	Odds ratio	95% confidence interval	*P*
Dialysis	3.74	1.62 - 8.65	0.002
Long operative time (> 5 hours)	3.44	1.38 - 8.56	0.008
Long-term intubation (> 48 hours)	7.83	3.70 - 16.60	< 0.001

Table 4. Logistic regression analysis of factors associated with PBSI

Factors	Odds ratio	95% confidence interval	*P*
Long-term intubation (> 48 hours)	17.8	6.67 - 47.70	< 0.001
Lack of POM	4.14	1.31 - 13.10	0.015

3. Factors associated with long-term intubation

Since long-term intubation was associated with PP and PBSI, we further analyzed the risk factors related to long-term intubation. Sixty-four patients (17.5%) had long-term intubation. According to univariate analysis, the factors associated with long-term intubation were age, NYHA class IV, reduced LVEF, emergency status, combined valvular disease, dialysis, long operative time, and lack of POM (Table 5). Logistic regression analysis identified four risk factors for long-term intubation: emergency status, combined valvular disease, long operative time, and lack of POM (Table 6). ROC analysis showed that AUC was 0.788 (95% confidence interval; 0.724-0.852).

Table 5. Univariate analysis of factors associated with long-term intubation

Factors	Number (%)		*P*
	long-term intubation (-)	long-term intubation (+)	
Age (> 65)	189 (62.8)	49 (76.6)	0.043
Sex (male)	159 (52.8)	31 (48.4)	0.582
Body Surface Area (> 1.8 m^2)	41 (13.6)	9 (14.1)	1.000
NYHA class IV	45 (15.0)	20 (31.2)	0.004
Reduced LVEF (< 50%)	63 (20.9)	25 (39.1)	0.003
Emergency status	39 (13.0)	25 (39.1)	< 0.001
Combined valvular disease	93 (30.9)	30 (46.9)	0.019
Concomitant coronary artery bypass grafting	61 (20.3)	19 (29.7)	0.133
Past cardiac surgery experience	40 (15.7)	14 (24.6)	0.123
IE	33 (11.0)	9 (14.1)	0.517
Hypertension	199 (66.1)	36 (56.2)	0.151
Diabetes	32 (10.6)	8 (12.5)	0.661
Dialysis	38 (12.6)	15 (23.4)	0.032
Long operative time (> 5 hours)	143 (47.5)	50 (78.1)	< 0.001
Lack of POM	142 (47.2)	43 (67.2)	0.004

Table 6. Logistic regression analysis of factors associated with long-term intubation

Factors	Odds ratio	95% confidence interval	*P*
Emergency status	4.65	2.39 – 9.05	< 0.001
Combined valvular disease	2.24	1.18 – 4.04	0.001
Long operative time (> 5 hours)	3.63	1.86 - 7.06	< 0.001
Lack of POM	2.18	1.21 - 4.16	0.013

Discussion

In the present study, we conducted an exploratory factor analysis using multivariate analysis. The significant finding of this study is that lack of POM could be a risk factor for PBSI following heart valve surgery. BSI is a common complication after cardiac surgery. A previous study reported a shorter duration of high fever in heart valve replacement patients who received preoperative periodontal treatment [22]. Bacteremia can be induced following gingival bleeding during tooth brushing and chewing in daily life [13, 14, 23]. Therefore, preoperative dental checkups are recommended for patients undergoing cardiac surgery [15]. Our results indicate that improving oral health before heart valve surgery is important to prevent PBSI. In addition to a lack of POM, long-term intubation was also shown to be a risk factor for PBSI. In a previous prospective study of 5158 patients, ventilation exceeding 48 hours was associated with an increased risk of postoperative infection including BSI and endocarditis [20]. Our results coincide with this finding. Long-term intubation induces decrease in stimulated salivary flow, which may contribute to the development of mucositis [24]. Once bleeding occurs from inflamed mucous membranes, oral microorganisms can easily enter the bloodstream. In addition, long-term intubation causes traumatic ulcers [25], the surface of which could be the entrance of oral microorganisms into bloodstream.

Regarding the incidence of long-term intubation, emergency status, combined valvular disease, long operative time, and lack of POM were identified to be risk factors. Long-term intubation has been shown to be significantly associated with mortality and complications after cardiac surgery [20, 26]. Regarding oral condition, Bágyi *et al*. [27] reported that untreated teeth and periodontal disease are risk factors for postoperative respiratory infections, which may cause long-term intubation. In addition, the longer the intubation period lasts, the greater the risk of dysphagia after endotracheal tube removal [28]. To improve these high-risk conditions, POM is necessary to prevent long-term intubation. In addition to a lack of POM, emergency status, combined valvular disease, and long operative time were also shown to be risk factors for long-term intubation. Patients in an emergency state are in a poor general condition, and combined heart valve surgery is more invasive than single heart valve surgery; these types of patients may have increased risk of long-term intubation. Longer surgery has been demonstrated to be a risk factor for postoperative infection in cardiac surgery [20]. Considering that postoperative infection is associated with prolonged mechanical ventilation after surgery [26], long operative time may also be a risk factor for long-term intubation.

Regarding the incidence of PP, univariate analysis showed that lack of POM was associated with it, but multivariate analysis did not identify the lack of POM as a risk factor. Inhibitory effects of POM on the incidence of PP have been demonstrated in cancer surgery [6, 7] and cardiac surgery [16]. In these reports, long-term intubation was not included as a factor to be analyzed. In the present study, long-term intubation was identified as a risk factor for PP and PBSI incidence, implying that it could be a critical factor associated with postoperative complications of cardiac surgery. The difference in the effect of POM in PP incidence seen in these studies seems to be caused by the difference in clinical factors analyzed.

Our study has several limitations. First, the study design was a single-center, retrospective observational study, which may limit the generalizability of the findings. Large-scale research by multiple centers will be required in the future. Second, factors regarding oral conditions including the number of teeth and oral hygiene status were not included. This is because no oral information was available for patients who did not receive POM. In the future, we plan to survey oral conditions in detail. Third, there were significant differences in two parameters of emergency status and hypertension between two groups, which may be possible confounding factors. In addition, data on socio-economic status were not available from medical records. In the future, we need to correct these data and adjust all background covariates to improve the results.

We conducted an exploratory factor analysis of postoperative complications of heart valve surgery. The results suggest that the lack of POM may be a risk factor for PBSI and long-term intubation. Therefore, it is recommended that patients undergoing heart valve surgery should receive POM to prevent postoperative complications.

Chapter 2

Effect of perioperative oral management on postoperative bloodstream infection in heart valve surgery patients

Subjects and Methods

1. Study design

This investigation was single-center, retrospective and observational in design. The study protocol was approved by the ethics committee of the Kagoshima University Graduate School of Medical and Dental Sciences (number: 190057).

2. Subjects

The medical record of 365 adult patients who underwent heart valve surgery at Kagoshima University Hospital from April 1, 2010, to March 31, 2019, were reviewed in this study. Sixty-four patients who underwent emergency surgery were excluded since preoperative oral management was not performed. Finally, 301 subjects were included in this study (Fig. 2), and the follow-up was conducted in the hospital. Table 7 shows the operative methods of heart valve surgery performed on the patients in this study.

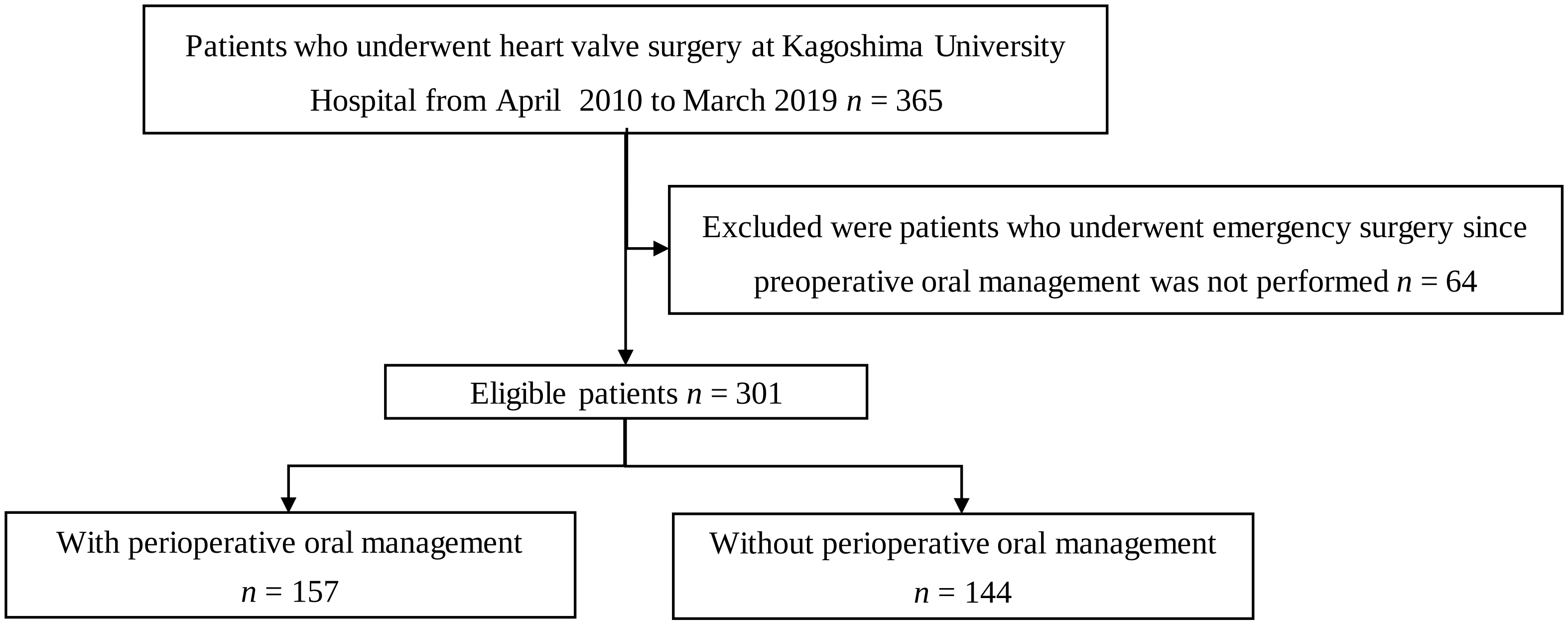

Fig. 2 Flowchart showing patient selection

Table 7. Operative methods and the number of patients

Aortic valve replacement	Mitral valvuloplasty	Mitral valve replacement	Tricuspid valvuloplasty	Tricuspid valve replacement	Concomitant coronary artery bypass	Number of patients
✓	✓		✓			9
✓	✓				✓	4
✓	✓					7
✓		✓	✓		✓	1
✓		✓	✓			19
✓		✓			✓	3
✓		✓				9
✓			✓			3
✓					✓	32
✓						114
	✓		✓		✓	5
	✓		✓			27
	✓			✓		1
	✓				✓	14
	✓					20
		✓	✓		✓	2
		✓	✓			16
		✓		✓		1
		✓			✓	4
		✓				10

3. Perioperative oral management

Of 301 subjects, 157 patients received POM. POM was performed on patients who agreed to receive it. The contents are the same as in **Chapter 1**.

4. Outcomes

The doctors diagnosed outcomes; PBSI, PP, and mortality. The definitions of PBSI and PP are the same as in **Chapter 1**. The mortality indicates that the patient died during the hospitalization period. In addition, we set death attributable to infection as an outcome.

5. Variables

POM covariates were extracted from medical records according to the reported risk factors for valvular heart disease [3-5, 20]. Age, sex, body surface area (m^2), creatinine (mg/dl), aortic valve disease, mitral valve disease, tricuspid valve disease, atrial fibrillation, concomitant coronary artery bypass grafting, past cardiac surgery experience, IE, NYHA functional classification, LVEF (%), hypertension, diabetes, cerebrovascular disease, chronic lung disease, dialysis, peripheral vascular disease, immunosuppressive treatment, operative time (> 5 hours), and intubation time (> 48 hours) were extracted as covariates. Hypertension was defined as use of anti-hypertensive medication before admission or confirmed blood pressure ≥ 140/90 mmHg. Diabetes mellitus was defined as a hemoglobin A1c level ≥ 6.5%, fasting blood glucose level ≥ 126 mg/dl, or use of anti-diabetes medication. There was no data loss for any of these factors.

6. Data analysis

The statistical methods used were propensity score (PS) inverse probability of treatment weighting (IPTW) [29-31]. Confounding factors often cause problems in retrospective observational studies; therefore, we minimized their effect by using the PS. PS refers to the probability that each patient is selected for treatment. First, we performed a logistic regression analysis to calculate the PS for POM. Next, the AUC of the PS was evaluated by ROC curve analysis. In IPTW, the treated group is weighted by the inverse of PS, and the untreated group is weighted by the inverse of 1-PS. Weighting was performed, and the standardized difference was calculated. Then a generalized linear analysis was performed to assess outcomes. In this study, the statistical significance level was set at 5%. IBM SPSS statistics version 26 (IBM, Tokyo, Japan) was used for analysis.

Results

1. Characteristics before and after adjustment by PS

Table 8 shows differences in the baseline characteristics between the POM and control groups. We analyzed categorical variables by the χ^2-test and continuous variables by Student's *t*-test, Welch's *t*-test or the Mann-Whitney *U*-test as appropriate. Regarding the relationship between operative methods and the outcomes, no significant differences were observed in the incidence of postoperative complications between patients who received total cardiac valve replacement and those received heart valve surgery other than total valve replacement (Table 9).

Table 8. Patient demographic and clinical characteristics at baseline

Factors and outcomes	POM group (n = 157)	Control group (n = 144)	*P*	Standardized difference
Age	68 (60-77)*	72 (63-77)*	0.173	0.194
Sex (male)	79 (50.3)	79 (54.9)	0.430	0.092
Body Surface Area (m^2)	1.56 (0.183)†	1.54 (0.191)†	0.501	0.107
Creatinine (mg/dl)	0.95 (0.77-1.25)*	0.97 (0.77-1.39)*	0.604	0.174
Aortic valve disease	100 (63.7)	101 (70.1)	0.236	0.136
Mitral valve disease	83 (52.9)	69 (47.9)	0.391	0.100
Tricuspid valve disease	46 (29.3)	38 (26.4)	0.574	0.065
Atrial fibrillation	33 (21.0)	19 (13.2)	0.073	0.208
Concomitant coronary artery bypass grafting	33 (21.0)	32 (22.2)	0.800	0.029
Past cardiac surgery experience	25 (15.9)	15 (10.4)	0.160	0.163
IE	14 (8.9)	7 (4.9)	0.168	0.158
NYHA class I	33 (21.0)	40 (27.8)	0.507	0.159
NYHA class II	59 (37.6)	45 (31.3)		0.133
NYHA class III	43 (27.4)	38 (26.4)		0.023
NYHA class IV	22 (14.0)	21 (14.6)		0.017
LVEF (%)	63.4 (51.9-71.4)*	60.7 (48.9-70.5)*	0.185	0.165
Hypertension	111 (70.7)	83 (57.6)	0.018	0.276
Diabetes	15 (9.6)	17 (11.8)	0.577	0.071

Cerebrovascular disease	7 (4.5)	3 (2.1)	0.340	0.135
Chronic lung disease	13 (8.3)	7 (4.9)	0.234	0.137
Dialysis	17 (10.8)	23 (16)	0.189	0.153
Peripheral vascular disease	8 (5.1)	11 (7.6)	0.365	0.103
Immunosuppressive treatment	8 (5.1)	6 (4.2)	0.702	0.043
Operative time (> 5 hours)	82 (52.2)	74 (51.4)	0.908	0.016
Intubation time (> 48 hours)	15 (9.6)	24 (16.7)	0.085	0.211
PBSI	4 (2.5)	10 (6.9)	0.070	0.209
PP	12 (7.6)	15 (10.4)	0.400	0.098
Mortality	3 (1.9)	11 (7.6)	0.018	0.270
Death attributable to infection	1 (0.6)	5 (3.5)	0.079	0.202

Values mean n (%) unless indicated otherwise; *values are median (25-75 percentile); †mean (standard deviation).

Table 9. Relationship between operative methods and outcomes

Outcomes	Valve replacement (+) group* (n = 235)	Valve replacement (-) group† (n = 66)	*P*
PBSI	12 (5.1)	2 (3.0)	0.479
PP	23 (9.8)	4 (6.1)	0.467
Mortality	11 (4.7)	3 (4.5)	0.963
Death attributable to infection	5 (2.1)	1 (1.5)	0.753

Values mean n (%).

*Patients who received total cardiac valve replacement.

†Patients who received heart valve surgery other than total valve replacement.

ROC analysis indicated that the AUC of the PS was 0.691. Table 10 shows the comparison of the factors between the two groups after IPTW. Since the P value after IPTW was more than 0.05 for all factors and the standardized difference after IPTW was less than 0.10 for all factors, the confounding factors could be adjusted [32].

Table 10. Patient demographic and clinical characteristics after IPTW

Factors and outcomes	POM group (n = 304 or 305)	Control group (n = 300 or 301)	*P*	Standardized difference
Age	70 (61-78)*	70 (62-77)*	0.720	< 0.001
Sex (male)	156 (51.3)	152 (50.5)	0.871	0.016
Body Surface Area (m^2)	1.55 (0.185)†	1.55 (0.190)†	0.501	0.011
Creatinine (mg/dl)	0.96 (0.77-1.36)*	0.95 (0.76-1.28)*	0.228	0.009
Aortic valve disease	205 (67.4)	218 (69.1)	0.663	0.037
Mitral valve disease	153 (50.3)	155 (51.5)	0.807	0.024
Tricuspid valve disease	89 (29.2)	87 (28.9)	1.000	0.007
Atrial fibrillation	52 (17.1)	49 (16.3)	0.828	0.021
Concomitant coronary artery bypass grafting	58 (19.1)	58 (19.3)	1.000	0.005
Past cardiac surgery experience	40 (13.2)	36 (12.0)	0.713	0.036
IE	23 (7.6)	26 (8.6)	0.657	0.037
NYHA class I	82 (26.9)	76 (25.3)	0.928	0.036
NYHA class II	102 (33.4)	97 (32.3)		0.023
NYHA class III	82 (26.9)	86 (28.7)		0.040
NYHA class IV	39 (12.8)	41 (13.7)		0.027
LVEF (%)	61.9 (50.0-71.3)*	61.5 (52.1-70.6)*	0.899	0.008
Hypertension	194 (63.8)	196 (65.1)	0.799	0.027
Diabetes	30 (9.9)	29 (9.7)	1.000	0.007
Cerebrovascular disease	10 (3.3)	9 (3.0)	1.000	0.017
Chronic lung disease	20 (6.6)	26 (8.6)	0.361	0.076

Dialysis	36 (11.8)	36 (12.0)	1.000	0.006
Peripheral vascular disease	20 (6.6)	18 (6.0)	0.867	0.025
Immunosuppressive treatment	14 (4.6)	19 (6.3)	0.376	0.075
Operative time (> 5 hours)	152 (49.8)	154 (51.2)	0.746	0.028
Intubation time (> 48 hours)	46 (15.1)	41 (13.6)	0.644	0.043

Values mean n (%) unless indicated otherwise; *values are median (25-75 percentile); †mean (standard deviation).

2. Incidence of complications after IPTW

Table 11 shows a result of generalized linear analysis for outcomes after IPTW. Patients in the POM group had a lower incidence of PBSI than the control group, with an odds ratio of 0.316 (P = 0.003). The mortality was significantly lower in the POM group than in the control group (P = 0.023). Among mortality from all causes, death attributable to infection was also 0.150 times lower in the POM group than in the control group (P = 0.035). Although not significant, patients in the POM group tended to have a lower incidence of PP (P = 0.231) than that in the control group.

Table 11. Generalized linear analysis for outcomes after IPTW

Outcomes	Odds ratio*	95% confidence interval	*P*
PBSI	0.316	0.146-0.684	0.003
PP	0.714	0.411-1.239	0.231
Mortality	0.378	0.163-0.873	0.023
Death attributable to infection	0.150	0.026-0.875	0.035

*with reference to the control group

3. Detection of microbes in patients with PBSI

Table 12 shows the detection of microbes in the blood samples of patients with PBSI. PBSI was suspected and tested for microbial identification in 63 cases, and 14 were diagnosed as PBSI. *Staphylococcus* was most frequently detected in both groups, and several genera, including *Pseudomonas*, *Corynebacterium*, *Serratia*, and *Acinetobacter*, were not detected in the POM group.

Table 12. Detection of microbes in patients with PBSI

Genus	Frequency	
	POM group	Control group
Staphylococcus	4	5
Pseudomonas	0	4
Enterococcus	1	2
Klebsiella	2	1
Corynebacterium	0	2
Enterobacter	2	0
Serratia	0	1
Acinetobacter	0	1
Candida	1	1

4. Reason for patient's death

Fourteen patients died in the present study and 6 of them were infection-related (Table 13). Of infection-related death, 1 was in the POM group and 5 were in the control group.

Table 13. Reason for patient's death

Reason	POM group	Control group
Infection		
Septic shock	0	2
Sepsis	0	1
Heart failure with sepsis	1	0
Multiple organ failure due to infection	0	1
Pulmonary edema caused by infection	0	1
Others		
Heart failure	0	2
Left ventricular rupture	1	1
Acute lung injury	0	1
Abdominal aortic rupture	0	1
Encephalocele	0	1
Brain stem hemorrhage	1	0

Discussion

In this study, we demonstrated that POM significantly reduced the incidence of PBSI in patients who underwent heart valve surgery. We performed IPTW since the AUC was substantially high (0.691), and the data were analyzed. In recent years, PS analysis has become widely used. This is because the estimation of PS does not need to consider the problems of overfitting and multicollinearity of factors. In IPTW using PS, the distributions between the two groups are pseudo-consistent. In other words, IPTW has the advantage of increasing the apparent number of subjects (Table 10). Retrospective observational studies using PSs have been performed to examine the effect of POM on cancer surgery [6, 7, 10]. For cardiac surgery, Nishi *et al.* [17] analyzed data after PS matching to examine the effect of POM, although they did not include the incidence of PBSI. Body fever is closely associated with postoperative infections. Suzuki *et al*. [22] reported that preoperative periodontal treatment reduced the duration of high fever in patients receiving heart valve replacement. In the present investigation, we collected an increased number of cases and clinical factors compared to those in that study, and we set PBSI as an outcome. As a result, we obtained a new finding that POM reduced the incidence of PBSI to 0.316 times the likelihood. To our knowledge, this is the first study to have demonstrated the effect of POM on PBSI in cardiac surgery using the IPTW. A systematic review [33] reported that it is unclear whether postoperative outcomes (i.e., all-cause mortality, IE, postsurgical infection, and length of stay in the hospital) differ between patients who received dental treatment and those who did not, prior to cardiac valve surgery. We compared our results with those of the studies selected in this review. Bratel *et al*. [34] showed that dental treatment did not improve long-term survival and Nakamura *et al*. [35] demonstrated that timing of tooth extraction before heart valve surgery did not affect the in-hospital mortality. In the present study, we showed that POM was effective to reduce in-hospital mortality, though the long-term mortality was not examined. Hakeberg *et al*. [36] showed that preoperative dental treatment did not reduce the incidence of early complications after heart valve surgery, although the present study showed the effect of POM to reduce early postoperative complications. Other studies [37, 38] showed that dental care before cardiac valve surgery was ineffective to reduce the incidence of IE. In the present study, we set PBSI as an outcome, which develops to IE, and demonstrated the effect of POM to reduce the incidence of PBSI. The differences in the effects of preoperative dental treatment observed in those previous studies and our study seem to be due to the difference in analyzing methods used. We used IPTW to adjust the background factors, enabling to improve evidence level compared with the previous studies.

Several bacteria and fungi were detected in the blood samples of PBSI patients in this study (Table 12). These microbes inhabit the oral cavity and have been reported to cause opportunistic infections [39-41]. In the POM group, *Pseudomonas*, *Corynebacterium*, *Serratia*, and *Acinetobacter* were not detected, and these results could be due to the effect of POM. During POM, dentists examine and treat the oral condition, and dental hygienists improve oral hygiene before and after surgery. These procedures are effective in reducing the accumulation of oral microbes and seem mandatory to prevent PBSI in heart valve surgery.

Patients who developed PBSI were treated with antibiotics, but six patients eventually died. IPTW also showed lower mortality from infection in the POM group than in the control group. The results suggest that POM significantly reduces PBSI, and consequently reduces mortality from infection. These results are similar to those of a previous multicenter retrospective study on cancer surgeries [6], and suggest that the reduction in postoperative complications with POM leads to the reduction in mortality [20]. The incidence rate of PP was lower in the POM group than in the control group, although no significant differences were observed. PP is a common symptom in cardiovascular patients and is mainly caused by oral bacteria [42, 43]. The mortality in cardiac surgery patients is associated with the development of PP [16]. Our results might support the effect of POM on the reduction in PP in cardiac surgery patients, which has been demonstrated by a previous study [16].

This study design was a single-center, retrospective observational study, which may limit the generalizability of the findings. However, we standardized as many of the dental procedures provided by the dental practitioners as possible. In addition, to minimize unmeasured confounding factors, we extracted many factors according to those reported in previous studies. The appropriateness of the extracted factors will be verified in future studies.

We investigated the effects of POM on PBSI, PP, and mortality in heart valve surgery patients using IPTW. POM was significantly associated with a decreased incidence of PBSI and mortality. The results suggest that POM is beneficial to patients undergoing heart valve surgery for the prevention of PBSI and mortality.

Summary

1. We conducted an exploratory factor analysis of POM for postoperative complications of heart valve surgery.
2. Lack of POM was a risk factor for PBSI and long-term intubation in heart valve surgery.
3. We analyzed the effect of POM on the prevention of postoperative complications in heart valve surgery using the IPTW.
4. POM was significantly associated with decreased incidence of PBSI and mortality.
5. The results suggest that POM is beneficial to patients undergoing heart valve surgery for the prevention of postoperative complications.

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