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The Prophylactic Effect of Proton Pump Inhibitors Combined with Enteral Nutrition for Preventing Gastrointestinal Hemorrhage after Cardiovascular Surgery in High-Risk Patients

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ABSTRACT

Background: Gastrointestinal hemorrhage (GH) is one of the most serious complications after cardiovascular surgery. The aim of the study was to provide an optimal therapeutic strategy for preventing postoperative GH in high-risk patients. Methods: This retrospective case-control study included 188 adult patients at high risk of postoperative GH. These patients were divided into two groups based on a strategy for preventing postoperative GH: Group A (n = 97) received continuous intravenous infusion of proton-pump inhibitor (PPI) combined with early enteral nutrition, and Group B (n = 91) received a bolus intravenous infusion of PPI combined with late enteral nutrition. The clinical features of the groups were examined.

Results: The incidence of postoperative GH in the patients of group A was significantly lower than the patients in group B. The duration from the end of surgery to eating for the first time in the patients of group A was significantly shorter than in the patients of group B. A descending trend in 30-day mortality was observed in the patients of group A compared with group B, but no significant difference was found between the two groups.

Conclusion: Continuous intravenous infusion of PPI combined with early enteral nutrition could effectively prevent GH and reduce 30-day mortality after cardiovascular surgery in high-risk patients.

INTRODUCTION

Gastrointestinal hemorrhage is rare (0.3%-1.0%) but often fatal (8.8%-47.6%) [Andersson 2005; Rodriguez 2010; D'Ancona 2003; Krawiec 2017; Fan 2010; Chaudhry 2017] and is one of the most serious complications after cardiovascular surgery; its occurrence noticeably prolongs the duration of hospitalization and intensive care unit (ICU) stays and increases hospital costs and the rate of transfusion [D'Ancona 2003; Grus 2014; Ait Houssa 2007]. Gastrointestinal hemorrhage has been reported to be induced by surgical stress, imbalance of intestinal flora, ischemic necrosis of gastrointestinal mucosa and perioperative inflammation [Ohri 2006; Quenot 2009; Perugini 1997]. Prophylactic administration of proton pump inhibitors (PPI) or antacid agents that protect the gastrointestinal mucosal barrier have been considered to be the most important strategy to prevent postoperative gastrointestinal hemorrhage [Patel 2013]. However, some postoperative patients who received the recommended prophylactic strategy were still found to suffer from gastrointestinal hemorrhage, and some of them died from it. Therefore, it is very important to find a more effective multimodality prophylactic strategy of gastrointestinal hemorrhage that will improve the prognosis of patients after cardiovascular surgery.

METHODS

This single-center retrospective clinical case-control study included 188 high-risk patients who underwent cardiovascular surgeries in the Department of Cardiovascular Surgery, Fujian Medical University Union Hospital, between January 2017 and December 2017. The Ethics Committees of Fujian Medical University Union Hospital approved this retrospective study.

These patients were divided into two groups according to the prophylactic strategy for addressing gastrointestinal hemorrhage: Group A (n = 97) received a continuous intravenous infusion of PPI combined with early enteral nutrition, and Group B (n = 91) received a bolus intravenous infusion of PPI combined with late enteral nutrition (Figure 1). Omeprazole Sodium for Injection (Losec, 40 mg, AstraZeneca) was the PPI used for both groups. Patients in group A were administered PPI through continuous intravenous injection 80 mg qd for 3-7 days or more days, if the pathogenesis of the condition required it after surgery. Probiotics and enteral nutrition beginning with clear liquids and followed by oligopeptide and dietary fiber were provided to these patients by nasogastric tube or oral administration within 12-24 h after surgery, regardless of extubation. The patients lay in a supine position with 30 degrees of elevation and walked early. The dosage of vasoactive drugs was reduced as soon as possible if pathogenesis conditions permitted. Patients in group B were administered PPI through a bolus intravenous injection 40 mg bid for 3-7 days or more days, if pathogenetic condition required

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it and were fed through a nasogastric tube or by oral administration within 48 h after surgery or within 6 h after extubation. The remainder of the prophylactic protocols were similar to those used for the patients in the group A.

Timing of PPI Withdrawal

PPI was withdrawn under the following conditions: (1) The hemodynamics of the patients were stable after extubation and they could eat normally or be fed with enteral nutrition through a nasogastric tube without gastrointestinal symptoms such as abdominal pain, ventosityor dysphoria; (2) Death occurred during therapeutic process; (3) Adverse drugs reactions were detected that were intolerant and suspected to be associated with PPI.

Inclusion Criteria

Adult patients who underwent cardiovascular surgery with cardiopulmonary bypass (CPB) and had at least one of the high-risk factors mentioned in the gastrointestinal complications after cardiac surgery (GICS) score [Andersson 2010].

Exclusion Criteria

(1) Patients with active gastrointestinal bleeding within 4 weeks before surgery; (2) Patients with esophageal and gastric varices associated with preoperative cirrhosis with portal hypertension; (3) Patients with hereditary or acquired coagulopathy; (4) Patients with hemorrhage from hemorrhoid; (5) Patients with gastrointestinal bleeding from intestinal ischemic necrosis caused by mesenteric artery embolism; (6) Patients who died within 24 h after surgeries.

Diagnosis of Gastrointestinal Hemorrhage

(1) Patients with visible hematemesis or melena confirmed by the results of an OB test; (2) Patients with instable hemodynamics and a reduction in the concentration of hemoglobin in the peripheral blood; (3) Patients with a positive result from an OB test of the drainage of digestive juices, vomit or feces; (4) Patients with an active hemorrhagic focus (excluding Dieulafoy's disease or gastrointestinal tumor) on the surface of gastrointestinal mucosa, confirmed by endoscopic examination or digital subtraction angiography (DSA); (5) Patients with bleeding in the respiratory tract.

General Clinical Data

General clinical data included age, sex, body mass index (BMI), history of use of anticoagulants or antiplatelet agents, coagulation function, the Child-Pughscore, New York Heart Association (NYHA) class, underlying diseases including history of gastrointestinal disease, hypertension, diabetes, hyperlipidemia, coronary artery disease (CAD), stroke, active smoking, alcoholism, GICS score, and EuroSCORE II.

Surgical and Intraoperative Treatments

Surgical and intraoperative treatments included type of surgical correction, duration of surgery, cardiopulmonary bypass (CPB), aortic cross-clamping, hypothermic circulatory arrest (HCA) and thoracic closure, and intraoperative blood loss.

Laboratory Examination

The laboratory findings used were the worst results of the perioperative routine blood test, conventional coagulation function test and thromboelastography (TEG).

Postoperative Statistics

The postoperative conditions assessed included length from the end of the operation to eating for the first time, the length of time from the end of the operation to defecation for the first time, meteorism, nausea, vomiting, abdominal pain, diarrhea, constipation, headache, the result of the fecal OB test, the volume of postoperative thoracic drainage, the volume of the allogenetic transfusion including red blood cells, fresh frozen plasma, platelets and cryoprecipitation.

Pharmacotherapy

Medications assessed included vasoactive agents, anticoagulants, antiplatelet agents and high-dose glucocorticoids.

Mechanical Assistance

Mechanical assistance assessed included the application of an intraaortic balloon pump (IABP) or/and extracorporeal membrane oxygenation (ECMO).

Short-term Prognosis

The short-term prognosis considered 30-day postoperative mortality, the duration of postoperative mechanical ventilation, ICU stays and hospitalization, postoperative complications including low cardiac output syndrome (LCOT), renal dysfunction, hepatic dysfunction, sepsis, multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), pulmonary infection, stroke, hypoproteinemia, reoperation for bleeding, and hyperlactacidemia. The follow-up reviews were conducted every 6 months after discharge. In cases of death after discharge, the cause was ascertained with the relatives' permission.

Statistical Analysis

SPSS 19.0 software was used for statistical analyses. Descriptive statistical analyses, Wilcoxon rank sum tests and repeated-measures ANOVAs were used to analyze measurement data. The Pearson chi-square test and Fisher exact test were used to analyze the count data. The Kaplan-Meier method was used to plot the survival curves. Statistical significance was defined as $P < .05$.

RESULTS

General Clinical Data

In total, 188 adult patients at high risk of gastrointestinal hemorrhage after cardiovascular surgery were included in this retrospective study, including 126 cases of cardiac valvular disease (CVD), 32 cases of CAD, 17 cases of acute aortic dissection (AAD), 10 cases of congenital heart disease (CHD) and 3 cases of heart transplantation (HT) (Table 1).

Table 1. Clinical Data

	Group A (n = 97)	Group B (n = 91)	*P*
Protopathy, n (%)			
CVD	64 (66.0)	62 (68.1)	.754
CAD	18 (18.6)	14 (15.4)	.563
AAD	9 (9.3)	8 (8.8)	.907
CHD	4 (4.1)	6 (6.6)	.450
HT	2 (2.1)	1 (1.1)	1.000
Age	48.2 ± 12.4	49.7 ± 9.9	.298
Sex, n (%)			
Male	69 (71.1)	63 (69.2)	.776
Female	28 (28.9)	28 (30.8)	
BMI	21.8 ± 4.2	22.3 ± 3.8	.721
Pharmacotherapy, n (%)			
Anticoagulant drugs	8 (8.2)	5 (5.5)	.457
Antiplatelet drugs	21 (21.6)	18 (19.8)	.752
Child-Pugh score, n (%)			
1	83 (85.6)	79 (86.8)	1.000
2	13 (13.4)	12 (13.2)	
3	1 (1.0)	0 (0)	
4	0 (0)	0 (0)	
NYHA class, n (%)			
I	28 (28.9)	30 (35.3)	.868
II	56 (57.7)	49 (57.6)	
III	8 (8.2)	6 (7.1)	
IV	5 (5.2)	6 (6.6)	
Underlying diseases, n (%)			
Gastrointestinal disease	6 (6.1)	3 (4.3)	.501
Hypertension	21 (21.6)	16 (17.6)	.483
Diabetes	11 (11.3)	13 (14.3)	.545
Hyperlipidemia	9 (9.3)	6 (6.6)	.497
CHD	25 (25.8)	16 (17.6)	.174
Stroke	2 (2.1)	1 (1.1)	1.000
Active smoking	25 (25.8)	19 (20.9)	.428
>Alcoholism	0 (0)	1 (1.1)	.484
EuroSCORE II	6.2 ± 2.3	6.5 ± 2.5	.329
GICS score	12.5 ± 6.4	13.1 ± 6.0	.654
Conventional coagulation function test			
PT, s	13.4 ± 3.2	12.8 ± 3.9	.473
INR	1.06 ± 0.4	1.10 ± 0.8	.516
APTT, s	38.9 ± 7.2	36.6 ± 6.0	.210
TT, s	17.2 ± 4.5	18.3 ± 6.3	.398
Fib, g/L	3.2 ± 1.9	3.1 ± 2.8	.429
TEG			
R, s	6.6 ± 4.1	7.1 ± 5.3	.280
K, s	1.9 ± 0.6	2.1 ± 0.8	.578
Angle (degree)	60.2 ± 12.2	59.1 ± 7.9	.372
MA, mm	55.9 ± 9.2	60.2 ± 10.2	.121
LY30, %	2.1 ± 2.2	2.9 ± 3.1	.482
EPL, %	1.3 ± 1.0	1.9 ± 1.3	.552
Routine blood test			
WBC, $\times 10^9$/L	8.9 ± 6.7	9.8 ± 7.1	.413
Hb, g/L	121.2 ± 10.1	117.6 ± 9.9	.370
PLT, $\times 10^9$/L	201.9 ± 29.2	223.2 ± 36.7	.292

The primary analyses revealed that there were no significant differences between the patients in terms of general clinical features. CVD indicates cardiac valvular disease; CAD, coronary artery disease; CHD, congenital heart disease; HT, heart transplantation; AAD, acute aortic dissection; BMI, body mass index; NYHA, New York heart association; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial prothrombin time; TT, thrombin time; Fib, fibrinogen; TEG, thromboelastography; WBC, white blood cell; Hb, hemoglobin; PLT, platelet.

The strategy of a continuous intravenous infusion of PPI combined with early enteral nutrition was applied in 97 of the included patients (Group A, 97/188, 51.6%), and the strategy of a bolus intravenous infusion of PPI combined with late enteral nutrition was applied in the patients of a second group (Group B, 91/188, 48.4%). The primary analyses revealed that there were no significant differences between the patients in terms of protopathy, age, sex, BMI, drug history of anticoagulants or antiplatelet agents, coagulation function, the Child-Pugh score, NYHA class, underlying diseases including history of gastrointestinal disease, hypertension, diabetes, hyperlipidemia, CAD, stroke, active smoking, alcoholism, GICS score and EuroSCORE II (Table 1).

Surgical and Perioperative Treatments

The chi-square test revealed that there were no significant differences in the types of surgical correction between the patients in the two groups. Wilcoxon rank sum tests also indicated that the duration of surgery, CPB, aortic cross-clamping, HCA, thoracic closure and perioperational blood loss had no significant differences in the patients in these two groups (Table 2).

Laboratory Examination

Wilcoxon rank sum tests revealed that there were no significant differences in the results of the preoperative and

Table 2. Surgical and Intraoperative Treatments

	Group A (n = 97)	Group B (n = 91)	*P*
Surgery, min	201.7 ± 256.9	223.0 ± 199.7	.089
CPB, min	61.5 ± 121.8	70.8 ± 155.2	.101
Aortic cross-clamping, min	38.8 ± 89.1	45.1 ± 109.7	.091
HCA, min	9 (9.3)	8 (8.8)	.907
Blood loss, mL	504.9 ± 109.6	550.9 ± 205.8	.087
Allogenetic transfusion			
RBC, U	2.8 ± 7.9	3.0 ± 10.1	.452
FFP, mL	300.4 ± 56.3	347.1 ± 79.3	.088
PLT, U	1.2 ± 2.4	1.5 ± 2.9	.381
CP, U	2.3 ± 5.5	2.9 ± 6.9	.210

Pearson chi-square test and Wilcoxon rank sum test revealed that there were no significant differences in the surgical and intraoperative treatments between the patients in these two groups. CPB indicates cardiopulmonary bypass; HCA, hypothermic circulatory arrest; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet; CP, cryoprecipitation.

postoperative routine blood tests, conventional coagulation function test, and TEG between the two groups (Table 3).

Postoperative Statistics

Wilcoxon rank sum tests showed that the period of time from the end of surgery to eating for the first time for the patients of group A was significantly shorter than for the patients in group B (14.5 ± 5.9 h versus 20.9 ± 8.9, *P* = .001). However, we could not discover significant differences in the length of time from the end of surgery to defecation for the first time (29.1 ± 8.1 h versus 35.2 ± 10.1, *P* = .054). We also discovered no significant differences in the incidences of postoperative meteorism, nausea, vomiting, abdominal pain, diarrhea, constipation, headache and the result of the fecal OB test between the two groups. The incidence of gastrointestinal hemorrhage in all patients was 5.9% (11/188) and the incidences of gastrointestinal hemorrhage (1/97, 1.0% versus 10/91, 11.0%, *P* = .004) and hematemesis (1/97, 1.0% versus 7/91, 7.7%, *P* =.030) in the patients in group A were significantly higher than the incidences in group B. However, no significant difference was found in the rate of hematochezia (1/97, 1.0% versus 5/91, 5.5%, *P* = .109) between the two groups.

No significant differences in the prescribing rates of vasoactive agent, anticoagulants, antiplatelet agents and high-dose glucocorticoids were identified between the patients in these two groups. The rates of the use of IABP and/or ECMO were also confirmed to be similar between the two groups. The 30-day postoperative mortality in all the patients was 3.2% (6/188). The mortality in the patients of group A seemed to be lower than that in the patients of group B (1/97, 1.0% versus 5/91, 5.5%, *P* = .082), but we could not see any significant differences between the two groups. Moreover, the duration of postoperative mechanical ventilation, ICU stay and

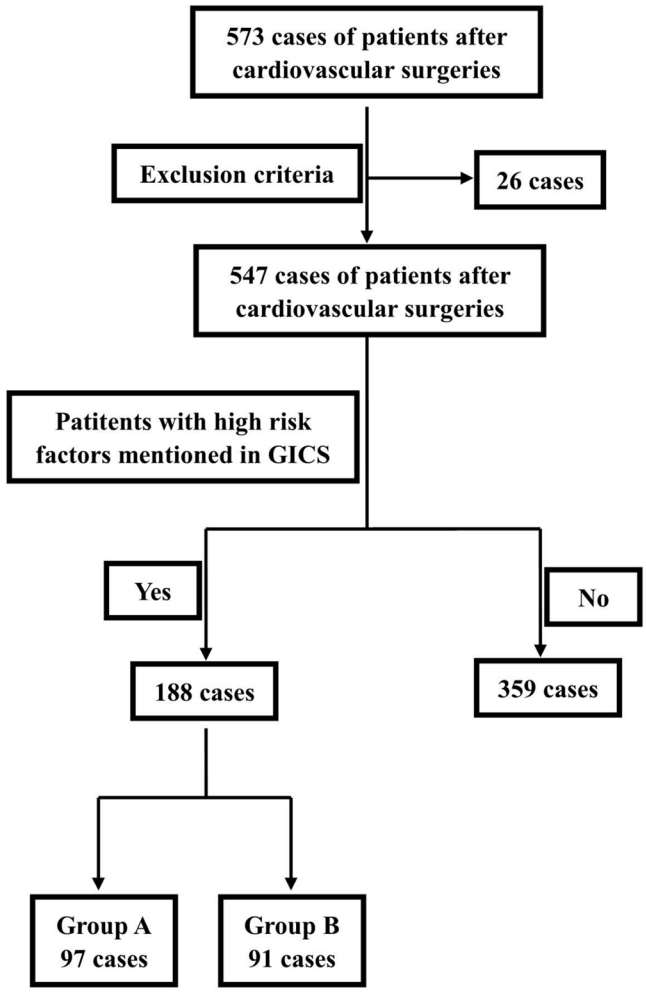

Figure 1. This study included 573 patients who underwent cardiovascular surgeries. Twenty-six patients who met the exclusion criteria were ruled out, and 188 cases that were consistent with at least one of the high-risk factors mentioned in the GICS score were divided into two groups according to the prophylactic strategy of gastrointestinal hemorrhage.

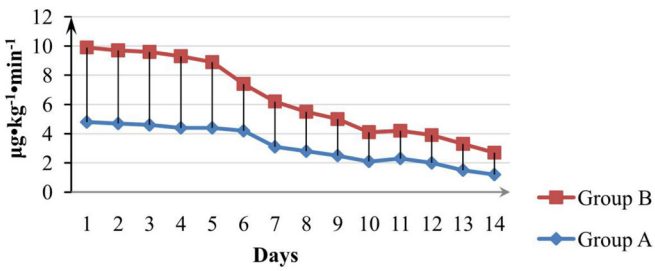

Figure 2. Repeated measures analysis revealed that the dosage of the postoperative dopamine of the patients in the two groups did not show significant differences within the 14 days after surgery (*P* = .578).

hospitalization were comparable, and we could not find any significant differences in the incidences of postoperative complications, excluding gastrointestinal hemorrhage between the two groups (Table 3; Figures 2, 3, 4, 5).

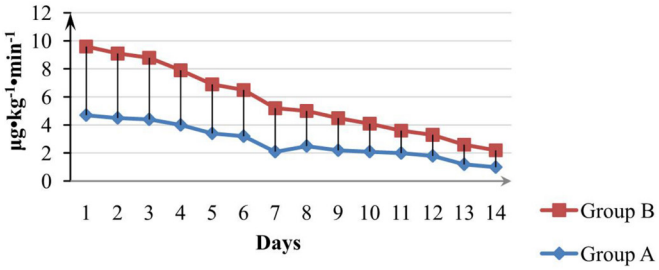

Figure 3. Repeated measures analysis revealed that the dosage of the postoperative dobutamine of the patients in the two groups did not show significant differences within the 14 days after surgery (P = .662).

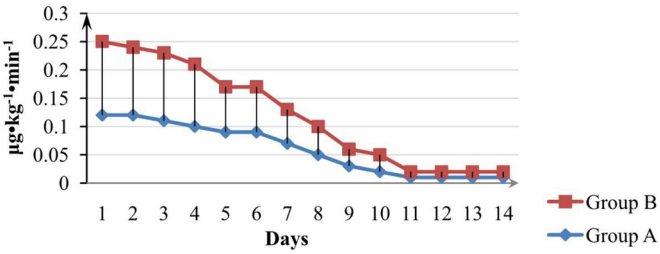

Figure 4. Repeated measures analysis revealed that the dosage of the postoperative adrenaline of the patients in the two groups did not show significant differences within the 14 days after surgery (P = .409).

Analysis of Patients with Postoperative Gastrointestinal Hemorrhage

Eleven patients with postoperative gastrointestinal hemorrhage (11/188, 5.9%) were observed in this research, and six of them (6/11, 54.4%) died within 30 days after their surgeries. The main causes of death were MODS (1 case from the patients in group A and 3 cases from the patients in group B) and LCOT (2 cases from patients in group B) (Table 4).

Survival Curves

Survival curve analyses based on 15 months of observation revealed no significant difference in the survival rate or the median survival time between the patients in group A and group B (Figure 6).

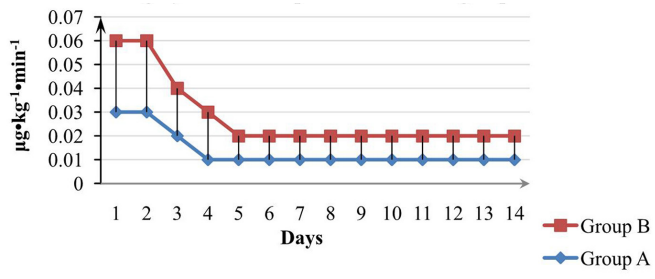

Figure 5. Repeated measures analysis revealed that the dosage of the postoperative noradrenaline of the patients in the two groups did not show significant differences within the 14 days after surgery (P = .781).

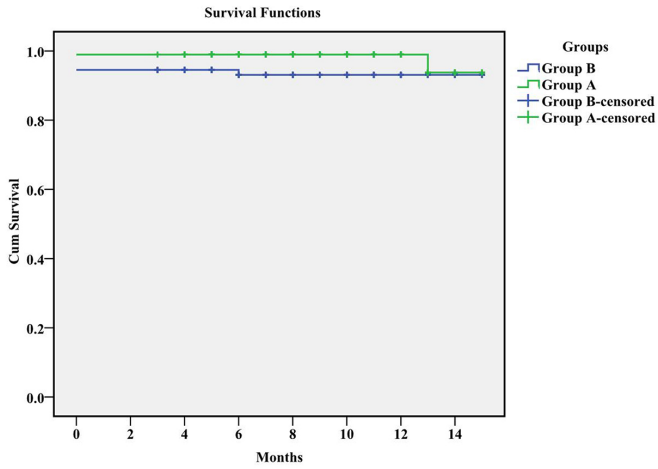

Figure 6. Kaplan-Meier plots reveal that there were no significant differences in the survival rates or the median survival times between the patients in group A and the patients in group B (log-rank result: χ^2 = 2.480, P = .115), (14.7 versus 14.0 months).

DISCUSSION

Gastrointestinal hemorrhage after cardiovascular surgery can be fatal and considerably difficult to diagnose early because of postoperative sedation, analgesia and mechanical ventilation. Thus, it is crucial for cardiovascular surgeons and physicians in the ICU to find an optimal therapeutic strategy to prevent gastrointestinal hemorrhage in high-risk patients after cardiovascular surgery. Currently, bolus intravenous infusion of PPI is a conventional prophylactic strategy for gastrointestinal hemorrhage after cardiovascular surgery [Madsen 2014]. However, in our research, 11% of patients suffered from postoperative gastrointestinal hemorrhage, and 50% of them died. Therefore, it is important to find a comprehensive therapy that would effectively prevent gastrointestinal hemorrhage after cardiovascular surgery and improve the outcomes of these patients.

Antacid agents used to play a key role in the empirical treatment to prevent gastrointestinal hemorrhage after cardiovascular surgery. However, certain questions need to be answered, including those concerned with choosing the dosage of the antacid agent and the timing of administration. According to our past experience, the strategy of using a bolus intravenous infusion of PPI did not effectively reduce the incidence of gastrointestinal hemorrhage after cardiovascular surgery. Thus, we improved the conventional treatment so that patients were administered PPI through continuous intravenous injection (80 mg qd) within 3-7 days after surgery, and PPI withdrawal was initiated when the hemodynamics of patients were stable after extubation and they could eat normally or be fed with enteral nutrition through a nasogastric tube without gastrointestinal symptoms such as abdominal pain, ventosity or dysphoria. The pH value of gastric mucosa could be continuously maintained above 6.0 with this modified antacid strategy without rebounding during the interval of bolus administration of PPI [Chwiesko 2016].

Table 3. Postoperative Statistics

	Group A (n = 97)	Group B (n = 91)	*P*
Eating for the first time, h	14.5 ± 5.9	20.9 ± 8.9	.001
Defecation for the first time, h	29.1 ± 8.1	35.2 ± 10.1	.054
Gastrointestinal symptoms, n (%)			
Hematemesis	1 (1.0)	7 (7.7)	.030
Hematochezia	1 (1.0)	5 (5.5)	.109
Gastrointestinal hemorrhage	1 (1.0)	10 (11.0)	.004
Meteorism	5 (5.2)	5 (5.5)	.917
Nausea or vomiting	9 (9.3)	11 (12.1)	.532
Abdominal pain	4 (4.1)	2 (2.2)	.683
Hematochezia	7 (7.2)	6 (6.6)	.866
Constipation	10 (10.3)	12 (13.2)	.540
Gastrointestinal hemorrhage for the first time, d	4.6 ± 3.4	5.2 ± 4.9	.361
Postoperative thoracic drainage, mL	892.2 ± 309.3	948.3 ± 403.1	.101
Anticoagulants, n (%)			
Warfarin	65 (67.0)	64 (70.3)	.624
Heparin	59 (60.8)	55 (60.4)	.957
Antiplatelet drug, n (%)	20 (20.6)	18 (19.8)	.886
high-dose glucocorticoids, n (%)	6 (6.2)	9 (9.9)	.349
Hypoproteinemia, n (%)	12 (12.4)	16 (17.6)	.316
Mechanical assistance, n (%)			
IABP	4 (4.1)	3 (3.3)	.765
ECMO	1 (1.0)	2 (2.2)	.611
Mechanical ventilation, h	15.9 ± 25.4	16.4 ± 28.5	.717
ICU stay, d	4.3 ± 11.2	5.6 ± 15.5	.538
Hospitalization, d	11.2 ± 19.4	13.1 ± 24.3	.228
30-day mortality, n (%)	1 (1.0)	5 (5.5)	.082
Postoperative complications, n (%)			
LCOT	4 (4.1)	4 (4.4)	.926
AKI requiring dialysis	8 (8.2)	9 (9.2)	.695
Child-Pugh score 3-4	7 (7.2)	8 (8.8)	.690
Sepsis	4 (4.1)	6 (6.6)	.451
MODS	2 (2.1)	6 (6.6)	.159
ARDS	3 (3.1)	3 (3.3)	.937
Pulmonary infection	12 (12.4)	18 (19.8)	.166
Stroke	2 (2.1)	2 (2.2)	1.000
Reoperation for bleeding	2 (2.1)	1 (1.1)	.599
Hypotension	7 (7.2)	10 (11.0)	.367
Lac>3 mmol/L	15 (15.5)	18 (19.8)	.437
Allogenetic transfusion			
RBC, U	2.9 ± 4.2	4.5 ± 5.9	.065
FFP, mL	302.3 ± 102.5	494 ± 192.7	.071
PLT, U	0.8 ± 0.5	1.1 ± 0.6	.075
CP, U	1.2 ± 2.2	2.0 ± 2.8	.093
Routine blood test			
WBC, $\times 10^9$/L	12.5 ± 5.3	12.9 ± 6.1	.478
Hb, g/L	11.0 ± 3.1	9.8 ± 5.7	.145
PLT, $\times 10^9$/L	159.6 ± 20.5	144.4 ± 39.3	.238
Conventional coagulation function test			
PT, s	14.3 ± 3.8	13.1 ± 4.9	.088
INR	1.09 ± 0.5	1.12 ± 1.0	.211
APTT, s	42.3 ± 6.5	46.6 ± 5.7	.322
TT, s	18.3 ± 4.0	18.5 ± 5.8	.836
Fib, g/L	3.8 ± 2.1	3.0 ± 3.8	.559
TEG			
R, s	6.7 ± 5.5	7.3 ± 4.6	.184
K, s	2.0 ± 0.5	2.0 ± 0.6	1.000
Angle (degree)	63.6 ± 15.3	66.9 ± 8.3	.112
MA, mm	59.2 ± 8.7	62.6 ± 9.1	.248
LY30, %	1.4 ± 1.2	1.9 ± 2.1	.234
EPL, %	1.2 ± 0.8	1.4 ± 1.0	.109

Wilcoxon rank sum tests showed that the length from the end of the operation to eating for the first time in the patients of group A was significantly shorter than the patients of group B. The incidences of gastrointestinal hemorrhage and hematemesis of the patients in group A were significantly higher than those in group B. The 30-day mortality in the patients of group A seemed to be lower than the patients of group B. IABP indicates intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; LCOT, low cardiac output syndrome; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; Lac, lactic acid; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet; CP, cryoprecipitation; WBC, white blood cell; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial prothrombin time; TT, thrombin time; Fib, fibrinogen; TEG, thrombelastogram.

Due to the complex pathogenic conditions of the patients after cardiovascular surgery, the administration of PPI alone is not sufficient to prevent gastrointestinal hemorrhage. Strategies for early eating have been reported to promote the recovery of gastrointestinal function through early enteral nutrition. Moreover, a lower incidence of intestinal flora imbalance has been observed in some studies with supplementation of intestinal probiotics after surgery [Marik 2010; Lee 2014; Lewis 2009]. In view of this, postoperative patients were fed probiotics and enteral nutrition through a nasogastric tube or by oral administration within 12-24 h after surgery, regardless of extubation. Wilcoxon rank sum tests

Table 4. Analysis of Patients with Postoperative Gastrointestinal Hemorrhage

	Group A (n = 1)	Group B (n = 10)	*P*
Protopathy, n (%)			
CAD	1 (100)	2 (20.0)	.273
AAD	0 (0)	3 (30.0)	1.000
CVD	0 (0)	5 (50.0)	1.000
Cause of death, n (%)			
MODS	1 (100)	3 (30.0)	.364
LCOT	0 (0)	2 (20.0)	1.000
30-day mortality, n (%)	1 (100)	5 (50.0)	1.000
Complications, n (%)			
CPR	0 (0)	1 (10.0)	1.000
IABP	1 (100)	1 (10.0)	.182
LCOT	1 (100)	2 (20.0)	.273
ECMO	0 (0)	2 (20.0)	1.000
AKI requiring dialysis	1 (100)	2 (20.0)	.273
Coagulopathy	0 (0)	1 (10.0)	1.000
Child-Pugh score>2	1 (100)	1 (10.0)	.182
Sepsis	0 (0)	2 (20.0)	1.000
MODS	1 (100)	5 (50.0)	1.000
ARDS	0 (0)	1 (10.0)	1.000
Pulmonary infection	1 (100)	5 (50.0)	1.000
Stroke	0 (0)	1 (10.0)	1.000

Eleven patients with postoperative gastrointestinal hemorrhage (11/188, 5.9%) were observed in this research, and 6 of them (6/11, 54.4%) were dead within 30 days after the operation. The main causes of deaths were MODS (1 case from patients in group A and 3 cases from patients in group B) and LCOT (2 cases from patients in group B). CAD indicates coronary artery disease; AAD, acute aortic dissection; CVD, cardiac valvular disease; MODS, multiple organ dysfunction syndrome; LCOT, low cardiac output syndrome; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome.

revealed that the length of time from the end of the operation to eating for the first time significantly decreased from 20.9 ± 8.9 h (group B) to 14.5 ± 5.9 h (group A).

It is worth noting that this new prophylactic treatment required coordination with our anesthesiologists, and short-acting sedation, muscle relaxants and analgesics should be used to accelerate the recovery of postoperative gastrointestinal function. Patients should be closely monitored and enteral nutrition should be stopped in the presence of ventosity, nausea, vomiting, abnormal borborygmus or an increase in gastric juices (cumulative volume >200 mL).

Using an inappropriate enteral nutrition strategy must be avoided for fear of aggravating the progress of postoperative recovery of the gastrointestinal function. Ten patients with gastrointestinal symptoms were observed in group A. This included six patients who were considered to be suffering from the residual effects of anesthesia and who recovered after symptomatic treatment; three patients who were considered to have gastrointestinal congestion induced by cardiac insufficiency and continued to receive enteral nutrition after the improvement of cardiac function; and one patient in whom the volume of nasogastric tube feeding was reduced due to postoperative MODS but who died within 10 days after surgery. All patients with postoperative gastrointestinal complications ultimately recovered and were discharged, excluding the one patient who died from MODS.

The analysis of clinical data revealed that there were no significant differences in the preoperative pathogenetic condition, protopathy, surgical and perioperative treatments, pharmacotherapy and postoperative complications. Therefore, we believed that the incidence of gastrointestinal hemorrhage could be effectively reduced by the new prophylactic strategy. Moreover, patients in group A showed lower 30-day postoperative mortality. However, no significant differences were found between the two groups, which could be explained by the small sample size. A similar phenomenon has been observed in the volume of perioperative transfusion between the patients in these two groups.

Interestingly, we did not find significant differences in the incidence of hematochezia in the patients in these two groups. However, hematemesis was significantly reduced in the patients in group A. This demonstrated that the new prophylactic strategy only maintained the integrity of the mucous bicarbonate barrier in the gastric mucosa and was inclined to protect the integrity of the upper gastrointestinal mucosa rather than lower gastrointestinal mucosa. In view of the limitations of this new prophylactic strategy, a more effective comprehensive treatment for the prevention of gastrointestinal hemorrhage should be the next goal of additional studies.

The major limitation of this study is the relatively small number of patients in whom gastrointestinal complications developed. Further validation requires a multicenter, randomized controlled study with a large sample size and long-term follow up.

Conclusion

Continuous intravenous infusion of PPI combined with early enteral nutrition could effectively prevent gastrointestinal hemorrhage and reduce 30-day mortality after cardiovascular surgery in high-risk patients. However, the new prophylactic strategy was inclined to protect the integrity of the upper gastrointestinal mucosa rather than that of the lower gastrointestinal mucosa. Further validation requires long-term follow-up and a multicenter, randomized controlled study with a large sample size.

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