Effect of Rabeprazole and Rebamipide in the Treatment of Upper Gastrointestinal Hemorrhage Associated with Dual Antiplatelet Therapy in Elderly Patients with Coronary Heart Disease

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Abstract
To investigate the therapeutic effect of rabeprazole and rebamipide on patient age over 60 with dual antiplatelet therapy (DAPT)–related upper gastrointestinal hemorrhage following percutaneous coronary intervention (PCI). A total of 360 patients age over 60 undergoing PCI were recruited for antiplatelet therapy involving a combined treatment of aspirin (100 mg/d) and clopidogrel (75 mg/d). The enrolled patients were divided into 4 groups: the control group, the rabeprazole group, the rebamipide group, and the rabeprazole + rebamipide group. The incidence and severity of any upper gastrointestinal hemorrhage and the incidence of major adverse cardiac events (MACEs) were observed 6 months after the operation. The incidence of upper gastrointestinal hemorrhage in the 4 groups was 11.1%, 3.3%, 8.9%, and 1.1%, respectively, and the differences were statistically significant ($P < 0.05$). On comparing the groups, the differences between the control group and the rabeprazole group, those between the control group and the rabeprazole + rebamipide group, and those between the rebamipide group and the rabeprazole + rebamipide group were found to be statistically significant ($P < 0.05$). The severity of the upper gastrointestinal hemorrhage in the rabeprazole group and the rabeprazole + rebamipide group was significantly lower than that in the control group. The 4 groups exhibited no significant differences in the incidence of MACEs ($P > 0.05$). For patients age over 60 receiving DAPT following PCI in our study population, treatment with rabeprazole or a combination of rabeprazole and rebamipide could reduce the risk of upper gastrointestinal hemorrhage, as well as reduce its severity.

Keywords
rabeprazole, rebamipide, aspirin, clopidogrel, upper gastrointestinal hemorrhage

Date received: 28 July 2022; revised: 7 September 2022; accepted: 16 September 2022.

Introduction
The number of patients with coronary atherosclerotic heart disease (CHD) in China has reached more than 11 million, while the burden of the disease continues to increase.1 Percutaneous coronary intervention (PCI) is the main treatment method for patients with CHD. The PCI technology in China has developed rapidly and the number of PCI-treated cases per year has reached almost 1 million.2 Adopting the dual antiplatelet therapy (DAPT) method following PCI to prevent thrombosis and in-stent restenosis and to reduce the incidence of major adverse cardiac events (MACEs) in patients has been recommended by

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numerous clinical investigations and multiple CHD-related guidelines and has become the cornerstone for the prevention of cardiac and systemic ischemic events in patients with CHD. Aspirin + clopidogrel is recommended as the DAPT strategy for most CHD patients following PCI, which is commonly recommended for 1–12 months according to the specific technique. However, DAPT can increase the risk of hemorrhage, which represents the most frequent noncardiac complication after PCI. And upper gastrointestinal bleeding is a common source of hemorrhage after PCI, especially in elderly patients, and may even lead to death. Therefore, it is crucial to prevent upper gastrointestinal hemorrhage in elderly patients with CHD who undergo DAPT.

The proton pump inhibitor (PPI) reduces the risk and severity of bleeding in the upper gastrointestinal tract by lowering the acidity in the gastric and duodenal lumen. Therefore, using a PPI is recommended by the latest guidelines to minimize upper gastrointestinal bleeding in patients receiving DAPT. However, the recommendation was relatively of “low-quality evidence” due to the lack of RCTs. With this in mind, this study observes the effects of a combined treatment involving the PPI, rabeprazole, and the gastric mucosal protective agent, rebamipide, in terms of the prevention and treatment of upper gastrointestinal hemorrhage associated with elderly DAPT patients.

Materials and methods

Patient Data

The clinical data of 360 patients age over 60 who underwent PCI in the 305 Hospital of Chinese PLA from May 2019 to December 2019 were retrospectively reviewed. The patients were aged from 60 to 84 years with an average age of 70.2 ± 5.5 years. Among them, 284 were males, and 76 were females. The following inclusion criteria applied:

1. Patients who underwent PCI and had at least one site of a coronary artery with 75% or more stenosis, as determined via elective coronary angiography.
2. Patients taking aspirin enteric-coated tablets (100 mg/d) and clopidogrel bisulfate tablets (75 mg/d) orally following the operation.
3. Patients willing to provide their informed consent to participate in the study.

The exclusion criteria included the following:

1. Patients with a malignant tumor.
2. Patients with hematological diseases.
3. Patients with portal hypertensive varices.
4. Patients with severe hepatic and renal insufficiency.
5. Patients with severe infection.
6. Patients with a history of gastrointestinal hemorrhage or bleeding in other areas within one year.
7. After an emergency PCI operation.
8. Patients who were allergic to antiplatelet agents.
9. Patients with dementia.

Implementation Methods

Based on the therapeutic methods, the patients were divided into the following 4 groups according to random digits table: i) the control group (90 cases), which included patients orally treated with aspirin enteric-coated tablets (Bayaspirin; 100 mg, once a day) and clopidogrel hydrogen sulfate tablets (Plavix; 75 mg, once a day) following PCI operation; ii) the rabeprazole group (90 cases), which included patients undergoing treatment based on DAPT, with the PPI, rabeprazole sodium enteric-coated capsules (Jinuo, Jichuan Pharmaceutical Group Co., Ltd, Approval No: SFDA Approval No.H20061220), taken orally from the first postoperative day (20 mg, 1/day, 30 min before breakfast); iii) the rebamipide group (90 cases), which included patients undergoing treatment based on DAPT, with the gastric mucosal protective agent, rebamipide (Mucosta, Zhejiang Otsuka Pharmaceutical Co., Ltd, Approval No: SFDA Approval No.H20020541), taken orally from the first postoperative day (100 mg, 3/day, 30 min before meals); and iv) the rabeprazole + rebamipide group (90 cases), which included patients receiving combined treatment with rabeprazole and rebamipide (same doses as above), taken orally from the first postoperative day, with the dosing maintained and the patients followed up for 6 months.

Observational index

The conditions regarding the postoperative upper gastrointestinal hemorrhage were observed in the patients, including in terms of positive fecal occult blood (excluding hemorrhoids), melena, and hematemesis. The severity of the upper gastrointestinal hemorrhage was divided into three levels: i) mild: no hematemesis, with only melena or fecal occult blood (++) or above, hemoglobin (Hb) levels of >100 g/L, and an identified blood loss volume of <500 ml; ii) moderate: hematemesis or melena, or Hb levels of 70–100 g/L, and an identified blood loss volume of 500–1000 ml; and iii) massive hemorrhage: hematemesis, melena, with changes in the peripheral circulation or Hb levels of <70 g/L, and an identified blood loss volume of >1000 ml.

The observational index of the Glasgow–Blatchford scale (GBS) bleeding score includes the following: blood urea nitrogen, Hb level, systolic blood pressure, pulse rate, and the existence of melena, syncope, hepatic disease, and heart failure. Various MACEs were also included, including cardiovascular death and recurrent non-fatal myocardial infarction, in which revascularization was needed involving secondary PCI or coronary artery bypass grafting.

Statistical Methods

The statistical analysis was conducted using SPSS 22.0 software, with the measurement data satisfying normal distribution.
expressed as means ± standard deviation. The analysis of variance method was used for inter-group comparisons. The countable data were tested using the χ² test and expressed in terms of number of cases and percentages. A P value of <0.05 was considered to be statistically significant.

Results

Comparison of the Baseline Characteristics among the Different Groups

The baseline characteristics in each group are shown in Table 1. The differences in gender, age, the existence of combined hypertension or type 2 diabetes mellitus, smoking history, and alcohol consumption history were not statistically significant among the groups (P > 0.05), and the data were comparable.

Comparison of the Incidence of Upper Gastrointestinal Hemorrhage among the Patients

The differences in the incidence of upper gastrointestinal hemorrhage within 6 months among the 4 groups were statistically significant (P = 0.016, <0.05), as shown in Table 2, with the incidence significantly higher in the control group than in both the rabeprazole group (P = 0.044, <0.05) and the rabeprazole + rebamipide group (P = 0.005, <0.05). Furthermore, the incidence of upper gastrointestinal hemorrhage within 6 months was significantly higher in the rebamipide group than in the rabeprazole + rebamipide group (P = 0.017, <0.05). However, the differences in the incidence of upper gastrointestinal hemorrhage within 6 months among the other groups were not statistically significant (P > 0.05), as shown in Table 3.

Comparison of the Upper Gastrointestinal Hemorrhage Severity among the Patients

The results of the comparison of the severity of the upper gastrointestinal hemorrhage among the 4 groups of patients are shown in Table 4. In the control group, the number of cases with mild, moderate, and severe hemorrhage was 2, 4, and 4, respectively, while in the rabeprazole group, there were 2 cases with mild hemorrhage and 1 case with moderate hemorrhage. In the rebamipide group, there were 3 cases of mild upper gastrointestinal hemorrhage and 5 of moderate upper gastrointestinal hemorrhage, while in the rabeprazole + rebamipide group, there was 1 case of mild hemorrhage. The severity of the gastrointestinal hemorrhage was significantly lower in the rabeprazole group and the rabeprazole + rebamipide group than in the control group. Besides in the rabeprazole group and the rabeprazole + rebamipide group, which is

| Table 1. Comparison of the Baseline Data among Groups. |
|--------------------------------------------------------|
| Group                                                  | Gender | Age (Year) | Hypertension | Diabetes mellitus | Smoking history | Alcohol consumption history |
|--------------------------------------------------------|--------|------------|--------------|------------------|-----------------|-----------------------------|
| The control group (n = 90)                             | Male   | 69.3 ± 5.4 | 67           | 33               | 66              | 55                          |
|                                                        | Female |            |              |                  |                 |                             |
| The rabeprazole group (n = 90)                          | Male   | 70.0 ± 5.5 | 69           | 30               | 62              | 51                          |
|                                                        | Female |            |              |                  |                 |                             |
| The rebamipide group (n = 90)                           | Male   | 69.0 ± 5.2 | 58           | 25               | 63              | 60                          |
|                                                        | Female |            |              |                  |                 |                             |
| The rabeprazole + rebamipide group (n = 90)             | Male   | 69.7 ± 4.9 | 68           | 32               | 65              | 54                          |
|                                                        | Female |            |              |                  |                 |                             |
| χ² or F value                                           | 0.667  | 0.433      | 4.318        | 1.900            | 0.541           | 1.964                       |
| P value                                                | 0.881  | 0.730      | 0.229        | 0.593            | 0.910           | 0.580                       |

| Table 2. Comparison of the Incidence Outcomes of Upper Gastrointestinal Hemorrhage among Groups. |
|--------------------------------------------------------------------------------------------------|
| Group                                                             | Frequency | Percent frequency |
|-------------------------------------------------------------------|-----------|-------------------|
| The control group (n = 90)                                        | 10        | 11.1%             |
| The rabeprazole group (n = 90)                                    | 3         | 3.3%              |
| The rebamipide group (n = 90)                                     | 8         | 8.9%              |
| The rabeprazole + rebamipide group (n = 90)                        | 1         | 1.1%              |
| χ² or F value                                                     | 10.264    |                   |
| P value                                                           | 0.016     |                   |

| Table 3. Comparison of the Incidence of Upper Gastrointestinal Hemorrhage among Groups. |
|----------------------------------------------------------------------------------------|
| Group                                          | χ²  | P         |
|------------------------------------------------|-----|-----------|
| ① versus ②                                   | 4.063 | 0.044     |
| ① versus ③                                   | 0.247 | 0.619     |
| ① versus ④                                   | 7.843 | 0.005     |
| ② versus ③                                   | 2.431 | 0.120     |
| ② versus ④                                   | 1.023 | 0.312     |
| ③ versus ④                                   | 5.731 | 0.017     |

Note: ①, the control group; ②, the rabeprazole group; ③, the rebamipide group; ④, the rabeprazole + rebamipide group.
almost expected, there was either no severe hemorrhage in the rebamipide group, and it was speculated that rebamipide could reduce the severity. The statistical analysis could not be conducted further due to the low number of cases in each subgroup following the division according to the severity of the hemorrhage.

The GBS prognostic scoring system can be adopted to assess the severity of the disease among patients with upper gastrointestinal hemorrhage to guide the follow-up treatment. Patients with a score of >6 points are considered to have moderate-to-high risk and those with a score of <6 points are considered to be at low risk.\(^{12-14}\) The upper gastrointestinal hemorrhage GBS scores of the patients in the control group, rabeprazole group, and rebamipide group were 10.00 ± 3.86, 3.67 ± 2.08, and 7.38 ± 1.51, respectively, while 1 case in the rabeprazole + rebamipide group had a GBS score of 2. The difference in the GBS scores in the control group and the rabeprazole group was statistically significant (\(P = 0.022, <0.05\)), while that between the control group and the rebamipide group was not statistically significant (\(P = 0.089, >0.05\)). This may be because the GBS score involves other factors, such as urea nitrogen, the existence of syncope, hepatic disease, and heart failure, except hematemesis, melena, or changes in Hb levels. The number of cases in the rabeprazole + rebamipide group was too low to analyze the difference in GBS score in relation to the control group. With reference to the comparison results (Table 4), it was deemed that the higher the GBS score, the greater the risk of severe hemorrhage.

### Table 4. Comparison of the Severity of Upper Gastrointestinal Hemorrhage among Groups.

| Group                              | Mild | Moderate | Severe |
|------------------------------------|------|----------|--------|
|                                    | Frequency | Percent frequency | Frequency | Percent frequency | Frequency | Percent frequency |
| The control group (n = 90)         | 2    | 2.2%     | 4      | 4.4%     | 4          | 4.4%       |
| The rabeprazole group (n = 90)     | 2    | 2.2%     | 1      | 1.1%     | 0          | 0%         |
| The rebamipide group (n = 90)      | 3    | 3.3%     | 5      | 5.5%     | 0          | 0%         |
| The rabeprazole + rebamipide group (n = 90) | 1    | 1.1%     | 0      | 0%       | 0          | 0%         |

### Table 5. Comparison Results of the Occurrence Time of Upper Gastrointestinal Hemorrhage among Groups.

| Group                              | <1 month | 1∼3 months | 3∼6 months |
|------------------------------------|----------|-------------|------------|
|                                    | Frequency | Percent frequency | Frequency | Percent frequency | Frequency | Percent frequency |
| The control group (n = 90)         | 2        | 20.0%       | 5          | 50.0%     | 3          | 30.0%       |
| The rabeprazole group (n = 90)     | 1        | 33.3%       | 2          | 66.7%     | 0          | 0%          |
| The rebamipide group (n = 90)      | 2        | 25.0%       | 5          | 50.0%     | 1          | 25.0%       |
| The rabeprazole + rebamipide group (n = 90) | 1        | 100%       | 0          | 0%        | 0          | 0%          |
| Total                              | 6        | 27.3%       | 12         | 54.5%     | 4          | 18.2%       |

\(\chi^2\) value 7.091
\(P\) value 0.030

Comparison of the Occurrence Time of Upper Gastrointestinal Hemorrhage among the Patients

As shown in Table 5, the total cases with upper gastrointestinal hemorrhage across the 4 groups was 22. Among them, there were 6 cases of upper gastrointestinal hemorrhage occurring within one month following PCI, 12 cases occurring within 1–3 months following the operation, and 4 cases occurring within 3–6 months after the operation. The differences in the occurrence time of upper gastrointestinal hemorrhage among the 4 groups were statistically significant (\(P = 0.030, <0.05\)), with the cases where the upper gastrointestinal hemorrhage occurred within three months following the operation accounting for 81.8% (18/22).

Comparison of the Incidence of major Adverse Cardiac Events among the Patients

As shown in Table 6, the differences in the incidence of MACEs were not statistically significant among the 4 groups (\(P = 0.194, >0.05\)), and it was deemed that neither the rabeprazole nor the rebamipide increased the incidence of cardiovascular events.

Discussion

Coronary heart disease is the primary cause of death and disability among elderly patients with cardiovascular disease.
Table 6. Comparison of the Incidence Outcomes of MACE among Groups.

| Group                                      | Frequency | Percent |
|--------------------------------------------|-----------|---------|
| The control group (n = 90)                | 6         | 6.7%    |
| The rabeprazole group (n = 90)            | 2         | 2.2%    |
| The rebamipide group (n = 90)             | 4         | 4.4%    |
| The rabeprazole + rebamipide group (n = 90)| 1         | 1.1%    |
| $\chi^2$ value                            | 4.708     |         |
| $P$ value                                  | 0.194     |         |

Many severely stenotic coronary arteries require PCI treatment to open the stenotic or occluded coronary arteries and restore the normal blood supply to the myocardium. Following PCI treatment, the standard long-term application of DAPT with aspirin and clopidogrel is an important measure for reducing the incidence of cardiovascular events. However, this therapy may inevitably result in the possibility of hemorrhagic-related complications, with upper gastrointestinal hemorrhage being the most common. One common adverse reaction of aspirin is gastric mucosal injury. Here, the pathological mechanism involves how the aspirin may inhibit the cyclooxygenase-1 and cyclooxygenase-2 activity, reduce the prostaglandins synthesis, and thereby weaken the action of the gastric mucosal barrier.15,16 Meanwhile, clopidogrel does not directly damage the gastrointestinal tract, but the active metabolites may inhibit the synthesis of angiogenic factors, thereby hindering the healing of a damaged gastric mucosa.15,16 Previous studies have demonstrated that upper gastrointestinal hemorrhage is an independent risk factor8,9 for death among CHD patients. In addition, antiplatelet agents may lead to adverse reactions, such as abdominal discomfort, which may reduce the patient’s compliance with regular medication, thereby increasing the risk of a recurrence of cardiovascular and cerebrovascular events.17

Given the above, the prevention of upper gastrointestinal mucosal injury and upper gastrointestinal hemorrhage is crucial for the long-term antithrombotic therapy in elderly CHD patients following PCI. The combined application of PPI preparations following PCI can not only reduce the risk of upper gastrointestinal hemorrhage but could also help to improve the upper gastrointestinal symptoms (eg, heartburn, acid reflux, upper abdominal pain) so as to increase the compliance among the patients to DAPT, and is thus of great significance in terms of preventing the occurrence of adverse cardiovascular events in patients following PCI.15,18,19

However, previous studies have demonstrated that PPI preparations may compete with clopidogrel to inhibit the cytochrome P450 isozyme, CYP2C19, thereby weakening the anti-platelet aggregation action of the clopidogrel, resulting in an increase in the incidence of MACEs, which is one of the independent risk factors for the occurrence of cardiac and cerebral ischemia events.19 However, rabeprazole differs from the traditional PPI preparations in that it does not depend on the cytochrome P450 enzymes and is mainly degraded by the non-enzymatic routes, meaning it has no clear interaction with clopidogrel and does not affect the latter’s antiplatelet function. As such, rabeprazole is a preferred option for antiplatelet therapy. In addition, the half-life of clopidogrel and its active metabolites in the plasma is extremely short, with a metabolic duration in the body of approximately 4–6 h, while the half-life of PPI preparations in the plasma is only 0.5–2 h. Thus, the administration of the two medicines at an interval of 12–15 h may, in theory, prevent the mutual influence. In clinical practice, the medication could be administered at different times, with, for example, the PPI preparations taken 30 min before breakfast and the clopidogrel taken before going to bed. By extending the time interval, the interaction between the two drugs could potentially be reduced.

In the present study, it was found that rebamipide could reduce the severity of gastrointestinal hemorrhage, which was deemed to be correlated with the increase in gastric mucosal blood flow and prostaglandin E2 content, as well as a reduction in the aspirin-induced damage to the gastric mucosal epithelial cells.20,21 However, the rebamipide group did not indicate a significant preventive effect on the occurrence of upper gastrointestinal hemorrhage in patients receiving DAPT following PCI. This was likely because the rebamipide had little effect on the basal gastric secretion and had no clear inhibitory effect on the stimulation of gastric acid secretion. Thus, the mono-therapy method may not effectively counteract the DAPT-related damage with a normal or even increased secretion of gastric acid.20,21

As a PPI preparation, rabeprazole could significantly inhibit gastric acid secretion, and largely eliminate the key factors of gastric mucosal damage, thereby reducing the incidence of upper gastrointestinal hemorrhage. However, rabeprazole cannot directly promote the healing of damaged gastric mucosa, meaning the combined use of rabeprazole and rebamipide could further prevent the occurrence of upper gastrointestinal hemorrhage in patients receiving DAPT following PCI. In addition, for the most part, the upper gastrointestinal hemorrhage occurred within three months after surgery. Therefore, the intervention therapy should be commenced from the first postoperative day and should be maintained for at least 3–6 months.

The present clinical trial also revealed that the additional use of rabeprazole combined with DAPT following PCI treatment in elderly patients with CHD could significantly reduce the incidence and severity of upper gastrointestinal hemorrhage. Furthermore, the combination of rabeprazole and rebamipide could further reduce the incidence of upper gastrointestinal hemorrhage, resulting in a synergistic effect of medications. However, the effect of rebamipide alone on preventing the occurrence of upper gastrointestinal hemorrhage was not clear, and the difference between the rebamipide group and the control group was not statistically significant, which further indicated that rabeprazole could play a key role in the
prevention of upper gastrointestinal hemorrhage following PCI in elderly CHD patients in terms of inhibiting the gastric acid secretion.

Given the relatively low number of cases in this clinical observation, the short follow-up duration following PCI (6 months), and the low number of cases involving moderate-to-severe upper gastrointestinal hemorrhage (GBS score ≥714), gastroscopy could be conducted to clarify the cause of the hemorrhage, while any cases involving the occurrence of gastrointestinal hemorrhage more than one year following PCI should be excluded. Future investigations could also focus on all patients with gastrointestinal hemorrhage following PCI, with gastrointestinal endoscopy conducted to clarify the specific site and etiology of the gastrointestinal hemorrhage, and to rule out the possibility of hemorrhage caused by a gastrointestinal tumor. In addition, for elderly patients who changed to clopidogrel-based monotherapy for antiplatelet complications after 1–2 years of maintenance therapy, whether continuing with rabeprazole treatment for the prevention of the occurrence of upper gastrointestinal hemorrhage is a good option should be investigated and statistically analyzed using controlled studies to further guide the prevention and diagnosis of upper gastrointestinal hemorrhage in elderly CHD patients and to improve the attendant treatment.

Declaration of Confl cting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article

Ethics Approval and Consent to Participate
This study was conducted with approval from the Ethics Committee of our hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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