Time of Resumption of Antiplatelet Drugs After Upper Gastrointestinal Hemorrhage

Huan Ma, Xiao Fan, Li Jiao, Xia Meng, Liwei Zhao, Junmin Wang

Corresponding Author: Huan Ma, e-mail: huanhuan19861216@126.com
Financial support: None declared
Conflict of interest: This research was supported by the Hebei Medical Science Research Project of China (No. 20210530)

Background: This study aimed to investigate the optimum time to reintroduce the original antiplatelet drugs after upper gastrointestinal hemorrhage in patients as secondary prevention for cardiovascular and cerebrovascular diseases.

Material/Methods: After the upper gastrointestinal bleeding stopped, patients were randomly divided according to the oral antiplatelet drugs administered. The aspirin group was further divided into 3-day and 7-day aspirin groups. The patients who took aspirin and clopidogrel were randomly divided into 3 groups: 0-day aspirin+3-day clopidogrel; 0-day aspirin+7-day clopidogrel; and 3-day aspirin+7-day clopidogrel. The recovery time, rebleeding rate, incidence of cardiovascular and cerebrovascular events, and death were observed.

Results: The 3-day aspirin group had more rebleeding, reduced risk of cardiovascular and cerebrovascular events, and a similar mortality rate compared to the other groups. In the aspirin+clopidogrel group, the 0-day aspirin+3-day clopidogrel group had the highest rebleeding rate and the lowest risk of cardiovascular and cerebrovascular events. The 3-day aspirin+7-day clopidogrel group had the highest risk of cardiovascular and cerebrovascular events and increased hospitalization time. The risk of rebleeding and cardiovascular and cerebrovascular events was lower in the 0-day aspirin+7-day clopidogrel group, and the overall mortality rate was the lowest in this group.

Conclusions: In patients receiving only aspirin, this drug should be reintroduced as soon as possible after peptic ulcer hemorrhage. Aspirin and clopidogrel are dual antiplatelet drugs used for the secondary prevention of cardiovascular diseases. In patients under dual-drug therapy, aspirin should not be stopped, while clopidogrel should be restarted in about 7 days.

Keywords: Aspirin • Clopidogrel • Gastrointestinal Hemorrhage

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/936953


Background

Antiplatelet drugs are the cornerstone for prevention and treatment of cardiovascular and cerebrovascular diseases. Antiplatelet drugs have also clear benefits in the secondary prevention of cardiovascular and cerebrovascular events [1]. On the other hand, antiplatelet treatment can have dual effects. For example, while reducing the incidence of cardiovascular and cerebrovascular events, it can also increase the risk of upper gastrointestinal bleeding. Some studies have shown that the use of antiplatelet drugs can increase the risk of gastrointestinal bleeding by 2-fold [2,3]. Since stopping antiplatelet treatment raises the risk of cardiovascular and cerebrovascular events, a crucial clinical issue is whether and how to discontinue prior antiplatelet treatments in patients with upper gastrointestinal bleeding. If antiplatelet medicines are not stopped, the original upper gastrointestinal bleeding might be aggravated or reoccur. For example, recent studies have shown that interrupting antithrombotic therapy after gastrointestinal bleeding can reverse the increased risk of ischemic events. Although resuming antithrombotic therapy can increase the risk of rebleeding, it can significantly reduce the incidence of thrombotic events and mortality [4-8]. Thus, clinical practice guidelines for treatment of nonvariceal upper gastrointestinal bleeding recommend the early resumption of antiplatelet therapy. However, there is no agreement regarding the optimal time at which to restart aspirin and/or other antiplatelet drugs [9-12].

In the present study, we evaluated how to reintroduce the original antiplatelet drugs after upper gastrointestinal bleeding in patients taking aspirin or aspirin plus clopidogrel. Additionally, we explored differences in cardiovascular and cerebrovascular events, rebleeding rate, and mortality between these 2 groups of patients. Finally, we discuss the best antiplatelet treatment strategy for patients after upper gastrointestinal bleeding.

Material and Methods

Case Selection

Data on patients that were hospitalized due to upper gastrointestinal bleeding from March 2020 to March 2021 were retrieved in the current study. As secondary prevention of cardiovascular and cerebrovascular diseases, the patients received aspirin (0.1 g/day) or aspirin (0.1 g/day) plus clopidogrel (75 mg/day). Electronic gastroscopy within 24 h showed a peptic ulcer and upper gastrointestinal bleeding was characterized as hematomecence, melena, or both, with a hemoglobin decrease of at least 2 g/dL. Upper gastrointestinal bleedings from other causes, such as esophageal and gastric varices rupture and bleeding, Mallord-Weiss syndrome, reflex esophagitis, esophageal cancer, gastric cancer, stromal tumor, pregnancy, and oral anticoagulants, were excluded. The protocol was approved by the Medical Ethics Committee of our hospital, and all patients signed the informed consent.

Treatment

After enrollment, all patients received PPI (esomeprazole) 80 mg static point, pumped with 8 mg/h for 3 days, then changed to esomeprazole 40 mg static point/day until discharge. Electronic gastroscopy was performed within 24 h after admission. Then, the Forrest grade was determined. This method consists of assessing the risk of rebleeding after peptic ulcer bleeding. It is divided into 3 levels: grades I, II, and III. Grade I is divided into stage Ia and stage Ib. Stage Ia includes ejection-like bleeding, and the probability of rebleeding is 55%. Stage Ib consists of active bleeding, and its recurrence probability is also 55%. Grade II includes 3 stages: Ila, IIb, and I lc. The bottom of the stage Ila ulcer has exposed blood vessels, and the risk of rebleeding is 43%. The bottom of the IIb ulcer has attached blood clots, and the risk of rebleeding is 22%. The bottom of the IIc ulcer is black, and the risk of rebleeding is 10%. Finally, the base of the stage III ulcer is clean, and the risk of rebleeding is 5%. Patients with Forrest grades Ia, Ib, and IIc received microscopic treatment consisting of hemostasis by endoscopic injection of drugs (including 1: 10 000 adrenaline or tissue glue) or a hemostatic clamp.

Random Grouping

After the upper digestive bleeding stopped, patients were randomly divided based on the oral antiplatelet drugs they received. Patients taking aspirin were randomly divided into 3-day and 7-day aspirin groups. Moreover, the patients receiving oral aspirin plus clopidogrel were randomly divided into 0-day aspirin+3-day clopidogrel, 0-day aspirin+7-day clopidogrel, and 3-day aspirin+7-day clopidogrel groups. Random grouping was performed using a computer-generated random number list. An independent person generated the random distribution sequence and distributed the same-design treatment package. The treatment package was unknown to patients and clinicians.

Observation Index and Test Endpoint

During hospitalization, the basic data, daily symptoms, hemoglobin changes, electronic gastroscopy, and the length of hospitalization were recorded. Patients were followed up twice outside the hospital for 28 days. The test endpoints were defined as follows: (A) Rebleeding: hematemesis, black stool after stool turned yellow, hemoglobin decreased by more than 2 g/dL within 24 h, or hemodynamic instability (heart rate >110 beats/min or systolic blood pressure <90 mmHg). The patients
who had rebleeding in the upper gastrointestinal tract needed a second electronic gastroscopy. (B) Cardiovascular and cerebrovascular events: acute coronary syndrome included unstable angina pectoris, non-ST segment elevation myocardial infarction, and ST segment elevation myocardial infarction; cerebrovascular events included acute cerebral infarction. (C) Death: death caused by cardiovascular and cerebrovascular events, and gastrointestinal complications.

Statistical Analyses

All statistical analyses were performed in SPSS17.0 statistical software. The Kaplan-Meier method was used to estimate the endpoint possibility of recurrent upper gastrointestinal bleeding within 28 days, as well as to compare all-cause mortality and the probability of cardiovascular and cerebrovascular events within 28 days in each group. The t test and χ²-test were applied to the measurement and count data.

Results

From March 2020 to March 2021, 148 individuals were enrolled. Among them, 90 received oral aspirin and were randomly divided into 3-day (n=45) and 7-day (n=45) aspirin groups. A total of 58 patients received oral aspirin plus clopidogrel and were randomly divided into 0-day aspirin+3-day clopidogrel (n=20), 0-day aspirin+7-day clopidogrel (n=19), and 3-day aspirin+7-day clopidogrel (n=19) groups. No significant difference was detected in the basic characteristics between the 2 groups (Table 1).

In the aspirin group, 1 patient (3-day aspirin group) presented upper gastrointestinal bleeding again (2.2%) confirmed by the second electronic gastroscope (multiple gastric ulcer bleeding). After endoscopic treatment, the patient did not bleed again. Four patients experienced cardiovascular and cerebrovascular events, 1 (3-day aspirin group) had unstable angina pectoris (2.2%). Among the other 3 patients (7-day aspirin group) (6.7%), 1 had an acute myocardial infarction, 1 had unstable angina pectoris, and 1 had acute cerebral infarction. No deaths occurred in either group. No significant difference was detected in stay length between the 2 groups (P=0.23) (Table 2).

In the aspirin plus clopidogrel group, 5 patients had recurrent upper gastrointestinal bleeding: 3 in the 0-day aspirin+3-day clopidogrel group (15%), 1 in the 3-day aspirin+7-day clopidogrel group (5.2%), and 1 in the 0-day aspirin+7-day clopidogrel group (5.2%). Four patients presented cardiovascular and cerebrovascular events, 3 in the 3-day aspirin+7-day clopidogrel group (15.7%), including 1 case of acute cerebral infarction, 1 case of unstable angina pectoris, and 1 case of acute
myocardial infarction. In the 0-day aspirin+7-day clopidogrel group (5.2%), 1 patient presented unstable angina pectoris. In the 0-day aspirin+3-day clopidogrel group, no cardiovascular or cerebrovascular events occurred, but 2 patients died: 1, assigned to the 3-day aspirin+7-day clopidogrel group (5.2%), was 89 years old and had an acute myocardial infarction and heart failure after upper gastrointestinal bleeding. The other patient, assigned to the 0-day aspirin+3-day clopidogrel group (5%), had a pulmonary infection after upper gastrointestinal bleeding. Furthermore, a significant difference was detected in the length of stay among the 3 groups. The length of stay in the 3-day aspirin+7-day clopidogrel group was significantly longer compared to the other 2 groups ($P=0.011$) (Table 2).

### Table 2. Number of rebleeding events, cardiovascular and cerebrovascular events, length of hospital stay, and deaths in each group.

| Observation index                      | Aspirin group 3-day group 7-day group | Aspirin combined with clopidogrel group 0+3-day group 3+7-day group 0+7-day group |
|----------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|
| Rebleeding, n(%)                       | 1 (2.2)                               | 3 (15.0)                                                                        |
| Length of stay, (SD)day                | 11.2 (3.4)                            | 14.7 (3.7)                                                                        |
| Cardiovascular and cerebrovascular diseases, n (%) | 1 (2.2) | 0 (0) | 3 (15.7) | 1 (5.2) |
| Acute coronary syndrome                | 1                                     | 2                                                                                | 0 | 1 |
| Acute cerebral infarction              | 0                                     | 1                                                                                | 0 |
| Death, n (%)                           | 0 (0)                                 | 1 (5.0)                                                                         |

The incidence of cardiovascular and cerebrovascular events within 28 days was not significantly different between the 2 aspirin groups (log-rank test, $P=0.310$). However, the overall incidence of cardiovascular and cerebrovascular events was lower in the 3-day group according to the survival curve (Figure 1).

Regarding patients that received aspirin plus clopidogrel, the 0-day aspirin+3-day clopidogrel group presented the highest incidence of rebleeding at 28 days, and the 3-day aspirin+7-day clopidogrel group presented the lowest. However, no significant difference was detected among the 3 groups (log-rank test, $P=0.344$, 0.337, and 0.984) (Figure 2). Then, the incidence of cardiovascular and cerebrovascular events was compared across groups. The 3-day aspirin+7-day clopidogrel group presented the highest incidence of events and the 0-day aspirin+3-day clopidogrel group presented the lowest. A significant difference was detected between these 2 groups (log-rank test, $P=0.045$), and no significant difference was detected between the other 2
groups (log-rank test, \(P=0.317\) and 0.297) (**Figure 3**). No deaths occurred in the 0-day aspirin+3-day clopidogrel group, and the mortality was similar in the 0-day aspirin+7-day clopidogrel and 3-day aspirin+7-day clopidogrel groups.

**Discussion**

To date, there is no consensus on the optimal time for the resumption of aspirin and/or other antiplatelet drugs. According to a previous meta-analysis, the time to develop acute coronary syndrome after stopping antithrombotic drugs is often less than 1 week, whereas the time to develop cerebrovascular events is generally less than 2 weeks. If aspirin is not administered for 5 days, 50% of the platelets in the circulatory system will be new platelets that can produce thromboxane, a significant factor in the development of thrombotic events [13]. Additionally, patients with upper gastrointestinal bleeding are more likely to have thrombosis [14,15]. Therefore, for patients with a high risk of recurrent bleeding, although aspirin can be temporarily stopped, it should be resumed within 5 days. According to a randomized controlled prospective study, patients who received low-dose aspirin for secondary prevention of cardiovascular diseases had a lower mortality rate than those who did not stop taking aspirin after peptic ulcer bleeding. In that study, 156 peptic ulcer bleeding patients who were taking low-dose aspirin as secondary prevention for cardiovascular diseases were enrolled, then randomly assigned to continue taking aspirin or to placebo groups. In week 8 of follow-up, the researchers found that the all-cause mortality of patients in the aspirin group was significantly lower compared to the placebo group (1.3% vs 12.9%, respectively) [4]. In a previous retrospective study, after using low-dose aspirin, 118 patients with bleeding peptic ulcers were followed up for 2 years. In that study, aspirin was stopped by 47 (40%) patients. The mortality rate in the group that stopped receiving aspirin was similar to that in the group that continued to receive oral aspirin (31%). However, a subgroup of patients had cardiovascular complications, and after stopping aspirin, the risk of death or acute cardiovascular events increased 4-fold [5]. Three recent retrospective investigations have found similar results. One study enrolled 544 patients with bleeding peptic ulcers, including 74 (13.6%) using oral anticoagulants. The risk ratio of thrombotic events after discontinuing anticoagulants was 10.9, and there was no statistically significant difference in the rebleeding rate between the 2 groups [6]. Similar results were found in another retrospective study, in which Cox risk analysis showed that the risk ratio of rebleeding in the anticoagulant withdrawal group was 2.98, but the risk ratio of death or acute cardiovascular events was 5.21 [7]. Finally, Siau et al evaluated 118 individuals who had upper gastrointestinal bleeding. When these patients were discharged from the hospital, they stopped the anticoagulant therapy. Stopping anticoagulants increased mortality, thrombotic events, and all-cause mortality, but did not increase the rebleeding rate [8]. In a 2019 study, 871 patients with gastrointestinal bleeding during the application of antiplatelet or anticoagulant drugs were enrolled. In that study, 38.9% of patients were treated with anticoagulants, 52.5% with antiplatelet drugs, 8.6% with both; 93.1% interrupted treatment after bleeding; 80.5% received the above treatment again within 7.6±36.4 days, 38.7% had upper gastrointestinal bleeding, 46.7% had lower gastrointestinal bleeding, and 14.6% had unknown causes of bleeding. The Cox model was used to evaluate rebleeding, vascular-related events, and mortality during 24.9 months. The use of anticoagulants or antiplatelet drugs increased the risk of bleeding while decreasing the risk of ischemia or death. Nevertheless, anticoagulant or antiplatelet treatment was resumed within 7 days, and mortality remained unchanged. Anticoagulant drugs increased the risk of bleeding more than antiplatelet drugs [16]. Overall, studies have suggested that aspirin should be taken as secondary prevention for cardiovascular diseases, and upper gastrointestinal bleeding should be stopped as soon as possible. Patients on dual antiplatelet drugs as secondary prevention for cardiovascular diseases should not stop taking aspirin, and, when present, the other antiplatelet drug should be resumed as soon as possible, but the optimal time remains unknown [17-19].

Herein, we found that patients with bleeding peptic ulcers using only aspirin should resume taking this drug as soon as possible. The incidence of cardiovascular and cerebrovascular events in the 3-day recovery group was lower than that in the 7-day recovery group. Although the incidence of rebleeding in the 3-day group was higher than that in the 7-day group, the mortality rate
did not change. After peptic ulcer bleeding in patients receiving aspirin and clopidogrel dual antiplatelet drugs, the incidence of cardiovascular and cerebrovascular events was significantly lower in the group with clopidogrel within 3 or 7 days without aspirin interruption compared to the group that resumed aspirin after 3 days. The risk of rebleeding was highest in the clopidogrel resumption group after 3 days without aspirin interruption, and the early mortality rate increased. Although 1 cardiovascular and cerebrovascular event was detected in the clopidogrel resumption group after 7 days, the mortality rate was the lowest.

Conclusions

In patients receiving only aspirin, this drug should be reintroduced as soon as possible after peptic ulcer hemorrhage.

The patients who were taking aspirin and clopidogrel dual antiplatelet drugs as the secondary prevention of cardiovascular diseases should not stop taking aspirin, and clopidogrel should be resumed in about 7 days.

Limitations

The number of cases was small, which might have led to data analysis deviations. The follow-up period was only 28 days, and the long-term prognosis of patients after drug administration was unknown. Finally, this was a single-center study, which might also have led to some deviations. Hence, a large-sample, multi-center, long-term follow-up study is required to confirm the present results.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part. SPSS17.0 statistical software was used to create all figures.

References:

1. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150:396-404
2. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-962
3. Lanas A, Carrera-Lasfuentes P, Arguedas V, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin Gastroenterol Hepatol. 2015;13:906-12
4. Sung JJY, Lau JYW, Ching JYL, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: A randomized trial. Ann Intern Med. 2010;152:1-9
5. Derogar M, Sandblom G, Lundell L, et al. Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. Clin Gastroenterol Hepatol. 2013;11:38-42
6. Kim SY, Hyun JJ, Suh SJ, et al. Risk of vascular thrombotic events following discontinuation of anti-thrombotics after peptic ulcer bleeding. J Clin Gastroenterol. 2016;50:e40-44
7. Wang XX, Dong B, Hong B, et al. Long-term prognosis in patients continuing taking anti-thrombotics after peptic ulcer bleeding. World J Gastroenterol. 2017;23:723-29
8. Slau K, Hannah JL, Hodson J, et al. Stopping anti-thrombotic therapy after acute upper gastrointestinal bleeding is associated with reduced survival. Postgrad Med J. 2018;94:137-42
9. Sung JI, Chiu PW, Chan FKL, et al. Asia-Pacific working group consensus on nonvariceal upper gastrointestinal bleeding: an update 2018. Gut 2018;67:1757-68
10. Gralnek IM, Stanley AJ, Morris AJ, et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline-Update 2021
11. Laursen SB, Jorgensen HS, Schaffaltzky de Muckadell OB, Danish Society of Gastroenterology and Hepatology. Management of bleeding gastrointestinal ulcers. Dan Med J. 2012;59:C4473
12. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47:a1-46
13. Patrono C, Morais J, Baigent C, et al. Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. J Am Coll Cardiol. 2017;70:1760-76
14. Lanas A, Dumonceau J-M, Hunt RH, et al. Nonvariceal upper gastrointestinal bleeding. Nat Rev Dis Primers. 2018;4:18020
15. Kyaw MH, Chan F. Managing antithrombotic agents in the setting of acute gastrointestinal bleeding. Gastrointest Endosc Clin N Am. 2018;28:351-61
16. Sostres C, Marchén B, Laredo V, et al. Risk of rebleeding, vascular events and death after gastrointestinal bleeding in anticoagulant and/or antiplatelet users. Aliment Pharmacol Ther. 2019;50:919-29
17. Halvorson S, Storey RF, Rocca B, et al. Management of antithrombotic therapy after bleeding in patients with coronary artery and/or atrial fibrillation: Expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2017;38:1455-62
18. Staerk L, Lip GY, Olesen IB, et al. Stroke and recurrent hemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: Nationwide cohort study. BMJ. 2015;351:h3876
19. González-Pérez A, Sáez ME, Johansson S, et al. Mortality in patients who discontinue low-dose acetylsalicylic acid therapy after upper gastrointestinal bleeding. Pharmacoepidemiol Drug Saf. 2017;26:215-22