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***Observational Study***

**Long-term effects on patients continuing antithrombotics after peptic ulcer bleeding**

Wang XX *et al*. Long-term effects on ulcer bleeding patients

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**Abstract**

***AIM***

To investigate the long-term prognosis in peptic ulcer patients who continue antithrombotics after ulcer bleeding, and determine risk factors that influence prognosis.

***METHODS***

All clinical information of peptic ulcer patients from January 1, 2009 to January 1, 2014 were retrospectively collected and analyzed. Patients were divided into two groups: continuing group, patients who continued antithrombotic drugs; discontinuing group, patients who discontinued antithrombotic drugs. The primary outcome of follow-up in peptic ulcer bleeding patients was recurrent bleeding, and secondary outcome was death or acute cardiovascular disease occurrence. The final follow-up of this study was December 31, 2014. Basic demographic data, complications and disease classifications were analyzed and compared by *t-* or *χ2*-test. The number of patients that achieved various outcomes was counted and analyzed statistically. A survival curve was drawn using the Kaplan-Meier method, and the difference was compared using the log-rank test. COX regression multivariate analysis was applied to analyze risk factors for the prognosis of peptic ulcer patients.

***RESULTS***

A total of 167 patients were enrolled into this study. As for the baseline information, differences in age, smoke and alcohol abuse, and acute cardiovascular diseases between the continuing and discontinuing groups were statistically significant (70.8 ± 11.4 *vs* 62.4 ± 12.0, *P* < 0.001; 8 (8.2%) *vs* 15 (21.7%), *P* < 0.05; 65 (66.3%) *vs* 13 (18.8%), *P* < 0.001). At the end of the study, 18 patients had recurrent bleeding and three patients died or had acute cardiovascular disease in the continuing group, while four patients had recurrent bleeding and 15 patients died or had acute cardiovascular disease in the discontinuing group. The difference in these results was statistically significant (*P* = 0.022, *P* = 0.000).The Kaplan-Meier survival curve indicated that the incidence of recurrent bleeding was higher in patients in the continuing group, and the risk of death and developing acute cardiovascular disease was higher patients in the discontinuing group. In addition, through log-rank test, the difference was statistically significant (*P* = 0.000, *P* = 0.000). Furthermore, COX regression multivariate analysis revealed that the hazard ratio (HR) for recurrent bleeding was 2.986 (95%CI: 067-8.356, *P* = 0.015) in the continuing group, while HR for death or acute cardiovascular disease was 5.216 (95%CI: 1.035-26.278, *P* = 0.028).

***CONCLUSION***

After the occurrence of peptic ulcer bleeding, continuing antithrombotics increases the risk of recurrent bleeding events, while discontinuing antithrombotics would increase the risk of death and developing cardiovascular disease. This suggests that clinicians should comprehensively consider the use of antithrombotics after peptic ulcer bleeding.

**Key words:** Peptic ulcer bleeding; Antithrombotics; Cardiovascular disease; Risk factor; Survival curve

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**Core tip:**Patients with peptic ulcer bleeding were enrolled into our study, and clinical information was analyzed by statistical method. We found that continuing antithrombotic drugs for peptic ulcer patients increased the risk of recurrent bleeding events, and discontinuing antithrombotic drugs increased the risk of death or cardiovascular events. Our results indicate that clinicians should balance the usage of antithrombotics in patients to reduce the risk of peptic ulcer bleeding.

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**INTRODUCTION**

Peptic ulcer has been broadly accepted as a medical illness to the public[1]. Furthermore, it also tremendously threatens the health of humans due to high morbidity and severe complications[2-5]. Among all complications, peptic ulcer bleeding is one of the common clinical diseases[6]. In recent years, since it has been widely known that the therapy of a disease blossoms on account of the application of proton pump inhibitors (PPI)[7-9] and *helicobacter pylori* eradication[10-12], which causes a slow increasing incidence, morbidity in patients with peptic ulcer bleeding has not decreased, based on relative literatures[13]. Furthermore, it has been reported that drugs aiming at antiplatelet, anticoagulation and thrombin inhibitors have recently been used extensively due to thromboembolic disease[14-16]. It has also been estimated that the usage of these drugs has been increasing worldwide as cardiovascular morbidity progresses in the aged population[17-18]. This would develop into a critical element that would induce a high incidence of peptic ulcer bleeding[19-20].Moreover, aspirin is one of antithrombotic drugs that have been widely applied in view of the benefit in preventing cardiovascular disease[21-22]. In addition, patients with cardiovascular disease should immediately prohibit the usage of aspirin after healing through the successful endoscopic treatment of peptic ulcer bleeding, in order to prevent death or acute disease occurrence, according to the Medication Guide[23]. Nevertheless, in a random and double-blinded study, Sung *et al*[24] found that recurrent bleeding events due to the continued usage of aspirin severely influences the prognosis of patients. Accordingly, there is an existing dilemma in clinical antithrombotic drugs usage. Furthermore, there are few studies on antithrombotics usage for treating peptic ulcer bleeding patients, and there is increasing concern on these patients in clinic. Hence, we collected the recent five-year clinical case data of patients with peptic ulcer bleeding in our hospital, aiming to investigate its effect on patients who continue the administration of antithrombotic drugs, including its prognosis risk factors. This would offer a fresh direction in the balanced application of antithrombotic drugs.

**MATERIALS AND METHODS**

***Study objects***

Patients with peptic ulcer in Tongren Hospital affiliated to Shanghai Jiao Tong University from January 1, 2009 to January 1, 2014 were included into this study. The study ended on December 31, 2014. Upper gastrointestinal hemorrhage was defined as hemoptysis, hematochezia, melena, fainting, or fainting at an early stage with anemia. Through screening, the following patients were excluded: patients with non-peptic ulcer bleeding, esophageal varices, vascular dysplasia, esophageal or gastric cancer, and ulcer perforation; patients with peptic ulcer bleeding who had an unsuccessful endoscopic treatment; patients who did not receive antithrombotic drugs after a successful therapy; patients who received proton pup inhibitors to prevent damage from antithrombotic drugs. The screening procedure is shown in Figure 1.

Through screening, a total of 167 patients were enrolled into this study. Patients were divided into two groups, based on whether drug administration was continued or discontinued after peptic ulcer bleeding was healed through endoscopic treatment: continuing group (*n* = 98), and discontinuing group (*n* = 69). The continuing group included patients who continued taking the drugs after the bleeding was healed, while the discontinuing group included patients who discontinued taking the drugs after the bleeding was healed. All patients in this study provided a signed informed consent, and this study was approved by the hospital ethics committee.

***Study methods***

The clinical data of patients including demographic data and complications were counted and analyzed by statistical method. The final time to end event was strictly calculated. Primary outcome was recurrent bleeding events within 30 d, including hemoptysis, melaena, > 2 g/dL of hemoglobin level within 24 hours, and unstable blood flow (systolic blood pressure ≤ 90 mm·Hg or heart rate ≥ 110 times/min). Patients with one of the aforementioned or combined characteristics were defined to achieve end events. Secondary outcomes were death or acute cardiovascular disease, death, acute myocardial infarction, and ischemia or transient ischemia. The number of disparate outcome patients was counted, and the difference was compared statistically. Survival time was collected to draw the survival rate, and the difference was compared by log-rank test. Multivariable COX proportional regression model was applied to analyze risk factors of the prognosis of peptic ulcer bleeding in patients.

***Statistical analysis***

All data of patients were analyzed using SPSS 19.0 software. Age, hemoglobin level and BMI measurements were expressed as mean ± SD. The number of smoke and alcohol abuse and cardiovascular patients was expressed as frequency. Normal distribution measurement data was compared by *t-*test. Frequency data was compared by *χ2*-test. Kaplan-meier was applied to calculate the survival rate and draw the survival curve. Differences were compared using the log-rank test. The multivariable COX proportional regression model was applied to analyze the risk factors of prognosis in patients with peptic ulcer bleeding. *P* < 0.05 was considered statistically significant.

**RESULTS**

***Clinical baseline data of patients with peptic ulcer bleeding***

After screening, a total of 167 patients with peptic ulcer bleeding were enrolled into this study. Among these patients, 98 patients continued receiving antithrombotic drugs, while 69 patients discontinued receiving antithrombotic drugs. The average age of patients who continued and discontinued receiving antithrombotic drugs was 70.8 ± 11.4 years and 62.4 ± 12.0 years, respectively. The difference was statistically significant (*P* = 0.000). Patients with a history of smoke and alcohol abuse was higher in the discontinuing group than in the continuing group (*P* = 0.012). Furthermore, complications of cardiovascular diseases was higher in the continuing group (*P* = 0.000; Table 1).

***Comparison various achieved outcomes between the two groups***

Recurrent bleeding occurred in 18 patients in the continuing group and four patients in the discontinuing group. Furthermore, death or acute cardiovascular disease occurred in three patients in the continuing group and 15 patients in the discontinuing group. Through the use of the *χ2-*test, the difference in primary and secondary outcome between the two groups was statistically significant (*P* = 0.018, *P* = 0.000; Table 2).

***Survival curve in the two groups***

Kaplan-Meier results indicated that bleeding occurred more frequently in patients in the continuing group, while survival rate was higher in patients in the discontinuing group. Log-rank test implied a statistical difference between the two groups (*P* = 0.022, *P* = 0.000; Figure 2).

***Risk factors analysis of the prognosis of patients***

The multivariable COX proportional regression model indicated that continuing the intake of antithrombotic drugs increased the risk of recurrent bleeding events (95%CI: 1.067-8.356, OR = 2.986, *P* = 0.015), while discontinuing the intake of antithrombotic drugs increased the risk of death or acute cardiovascular occurrence (95%CI: 1.035-26.278, OR = 5.216, *P* = 0.028; Table 3).

**DISCUSSION**

Peptic ulcer is one of the most common clinical gastrointestinal tract diseases at present[6,25],which is generally induced by damage in the gastric or duodenal mucous membrane. Gastric acid and protease plays a crucial role in disease progression[26,27]. The aged population occupies most of the proportion of the disease, and ulcer bleeding, perforation and pyloric obstruction are the most common complications[28-31]. Generally speaking, infection of *Helicobacter pylori*, excessive secretion of gastric acid, and excessive antithrombotic drug intake would trigger ulcer bleeding occurrence[32-34]. In recent years, peptic ulcer morbidity has slowly increased due to medical technology progression[35]. However, ulcer bleeding incidence rate has been continuously increasing[36,37].

Cardiovascular disease is defined as all tissues with ischemic or hemorrhagic disease on the account of atherosclerosis and blood viscosity[38]. In view of its high morbidity and mortality, more and more people, even healthy people, tend to take antithrombotics to prevent and reduce risk[39]. However, excessive drugs will increase bleeding risk instead in patients with ulcer bleeding, which raises concerns in clinic.

As the aged population increases with the necessity for preventing acute cardiovascular disease occurrence, aspirin and other antithrombotics continues to be broadly used in public; and these proportion has elevated rapidly[40-42]. It has been reported that most patients with established cardiovascular disease ignore the risk of aspirin, and continue to insist in taking aspirin or some antithrombotics for secondary prevention[43,44]. Even more, literatures have shown that cardiovascular disease complications occur more frequently in patients who have discontinued antiplatelet drug therapy, compared to patients who continued this therapy[45]. Nevertheless, continuing the intake of aspirin or antithrombotic drugs will increase hemorrhage complication risk in surgery instead[46,47]. Accordingly, clinicians could not balance the risk of cardiovascular disease and hemorrhage complications. In addition, there are few literatures on the prognosis of patients with peptic ulcer bleeding. Hence, the clinical data of patients with peptic ulcer bleeding in our hospital were collected and analyzed to discuss the prognosis of patients, hoping to provide guidance for clinical applications.

***Age and smoke and alcohol abuse influence the usage of antithrombotics in******patients with peptic ulcer bleeding***

Our study revealed that patients were older in the continuing group than in the discontinuing group, indicating that aged patients need more antithrombotics. This is consistent to the current social situation. The number of patients with cardiovascular disease complications was higher in the continuing group than in the discontinuing group, which accords with a previous report that patients with an established disease tend to continue taking drugs. In addition, there was a difference in smoke and alcohol abuse between the two groups; in which there were more patients in the discontinuing group. It is plausible that patients are taking drugs tend to reduce smoke or alcohol.

***Taking antithrombotics affects survival rate in patients with peptic ulcer bleeding***

Our study indicated that patients who continued to take the drugs had a higher risk of recurrent bleeding events. In contrast, patients in the discontinuing group had a higher risk of death or acute cardiovascular disease. In recent years, it has been reported that there was no difference between these two groups, which does not accord with our results. On one hand, our follow-up time did not have a limit. However, patients with less than two months of follow-up were excluded in the study conducted by Kim *et al*[48]Furthermore, it has been widely accepted that recurrent bleeding time was shorter than normal bleeding time. On the other hand, the number of patients in these two researches was disparate. However, it was consistent to our results that Sung *et al*[24]estimated a higher incidence of recurrent bleeding events in the continuing group in a random and double- blinded study, which has a likelihood ratio of nearly 2. Through retrospective research, we were also able obtain similar results, which further supported this view; which has a likelihood ratio of nearly 3[49]. This implies that more attention should be given when continuing antithrombotics.

***Limitations and prospects***

This time study also has some limitations. First, we limited number of patients that could not sufficiently support our conclusion. Second, we did not divide antithrombotic drugs to clear a part. However, more studies have shown that the single or combined application in the usage of drugs would induce disparate difference. Finally, we lack the definite segmented time of bleeding. Hence, we were not able to obtain the precise time when to discontinue or continue drugs.

 In conclusion, our results demonstrate that after the occurrence of peptic ulcer bleeding, continuing the intake of drugs would increase the risk of recurrent bleeding events, while discontinuing the intake of drugs will increase the risk of death and acute cardiovascular occurrence. These indicate that clinicians must extensively consider when using antithromboticsin treating patients with peptic ulcer bleeding.

**COMMENTS**

***Background***

Peptic ulcer is one of the most common clinical gastrointestinal tract diseases to date, which is generally induced by damage in gastric or duodenal mucous membrane. Gastric acid and protease plays a crucial role in disease progression. Aged population occupies most proportion of disease and ulcer bleeding, perforation and pyloric obstruction are the most common complications. Generally speaking, infection of helicobacter pylori, excessive secretion of gastric acid and excessive antithrombotic drugs taking would trigger ulcer bleeding occurrence. In recent years, peptic ulcer morbidity has increased slowly duo to medical technology progression, but ulcer bleeding incidence rate has been increasing all the time.

Cardiovascular disease is defined as all tissues ischemic or hemorrhagic disease on account of atherosclerosis, blood viscosity etc. In view of its high morbidity and mortality, more and more people even healthy people tend to take antithrombotics to prevent and reduce risk. However, excessive drugs will increase bleeding risk instead in ulcer bleeding patients which raises concern in clinical.

***Research frontiers***

As the aged population increases and necessity for preventing acute cardiovascular disease occurrence, aspirin and other antithrombotics are broadly used in public and proportion elevates rapidly. It is reported that most patients with established cardiovascular disease ignore risk of aspirin and still insist in taking aspirin or some antithrombotics for secondary prevention. Even more, there are literatures showing patients have cardiovascular disease complication more easily discontinuing antiplatelet drugs therapy compared to continuing antiplatelet drugs therapy. Nevertheless, continuing aspirin or antithrombotic drugs will increase hemorrhage complication risk in surgery instead. Accordingly, clinicians could not balance risk of cardiovascular disease and hemorrhage complication. Besides, literatures on prognosis of ulcer bleeding patients are not so much.

***Innovations and breakthroughs***

Our results was collected and analyzed retrospectively to investigate prognosis risk factors of peptic ulcer bleeding patients. Even more, we showed two survival curves with disparate outcomes to manifest survival rate difference in continuing or discontinuing patients. And with our results, clinicians must take more attention in usage of antithrombotic drugs.

***Applications***

This study demonstrates that after occurrence of peptic ulcer bleeding, continuing taking drugs will increase risk of recurrent bleeding events, discontinuing drugs will increase risk of death and acute cardiovascular occurrence, which indicates that clinicians must consider extensively when using antithrombotics to ulcer bleeding patients.

***Peer-review***

Patients with ulcer peptic bleeding were enrolled in our study and clinical information was analyzed by statistical method. We found that continuing antithrombotic drugs in ulcer peptic patients increased the risk of recurrent bleeding events and discontinuing drugs increased risk of death or cardiovascular events. Our results indicated that clinicians should balance usage of inpatients antithrombotics to reduce risk in peptic ulcer bleeding patients

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**Table 1 Baseline information comparison between the continuing and discontinuing groups *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic**  | **Continuing group** | **Discontinuing group** | ***T/χ2*** | ***P* vaule** |
| Patients  | 98 | 69 |  |  |
| Demography data |  |  |  |  |
| Gender (male/%)  | 68 (69.39) | 42 (60.87) | 1.307 | 0.253 |
| Age (mean ± SD) | 70.8 ± 11.4 | 62.4 ± 12.0 | 4.588 | 0.000 |
| BMI (kg/m2, mean ± SD) | 21.4 ± 4.5 | 22.0 ± 4.2 | 0.872 | 0.385 |
| Complications |  |  |  |  |
| Smoke and alcohol abuse | 8(8.2) | 15(21.7) | 6.284 | 0.012 |
| Diabetes | 32(32.7) | 15(21.7) | 2.385 | 0.123 |
| Hypertension  | 71(72.4) | 56(81.2) | 1.338 | 0.247 |
| Chronic kidney disease | 23(23.4) | 8(11.6) | 3.777 | 0.052 |
| Chronic obstructive pulmonary disease  | 10(10.2) | 8(11.6) | 0.081 | 0.775 |
| Acute cardiovascular disease | 65(66.3) | 13(18.8) | 36.681 | 0.000 |
| Non-antithrombotic drugs usage |  |  |  |  |
| Aspirin | 84(85.7) | 59(85.5) | 0.001 | 0.970 |
| Forrest classification |  |  |  |  |
| I-II | 31(31.6) | 28(40.6) | 1.419 | 0.234 |
| III | 67(68.4) | 41(59.4) | 1.419 | 0.234 |
| Hemoglobin(g/dl) | 9.0 ± 2.4 | 8.6 ± 2.1 | 1.116 | 0.266 |

**Table 2 Comparisonof various outcomes achievedbetween the two groups *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Continuing group** | **Discontinuing group** | ***χ2*** | ***P* vaule** |
| Recurrent ulcer bleeding events | 18 (18.4) | 4 (5.8) | 5.594 | 0.018 |
| Death or cardiovascular occurrence | 3 (3.1) | 15 (21.7) | 14.689 | 0.000 |

**Table 3 COX regression multivariate analysis of the risk factors of 176 patients with prognosis of bleeding**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Recurrent ulcer bleeding events** |  | **Death or cardiovascular occurrence** |
|  | **β** | **OR** | **95%CI** | ***P* value** |  | **β** | **OR** | **95%CI** | ***P* value** |
| Usage of antithrombotics | 1.094 | 2.986 | 1.067-8.356 | 0.015 |  | 1.652 | 5.216 | 1.035 -26.278 | 0.028 |



**Figure 1 Screening of patients with peptic ulcer.**



**Figure 2 Kaplan-Meier survivalcurvein various outcomes.**