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Assessment of Safety of Using Antithrombotic Agents during Esophagogastroduodenoscopy : Rationale and Design of the ASAMA Study

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Background : Guidelines for the management of anticoagulation and antiplatelet therapy during endoscopic procedures have been established by the Japanese Circulation Society and the Japan Gastroenterological Endoscopy Society. However, these Japanese guidelines are not in accordance with those of the American Society for Gastrointestinal Endoscopy (ASGE). The ASGE guidelines indicate that aspirin and warfarin may be continued for endoscopic procedures associated with a low risk of bleeding. In contrast, the Japanese guidelines recommend cessation of antithrombotic agents before endoscopy, even if the procedure is classified as low risk. In this trial, we investigate the feasibility of performing esophagogastroduodenoscopy (EGD) with biopsy without the cessation of antithrombotic agents in Japanese patients, in accordance with the ASGE guidelines.

Methods and Results : This investigation is a prospective, non-randomized, multicenter trial of patients who undergo scheduled EGD with biopsy while under antithrombotic therapy. Patients will either continue to take antithrombotic agents (group A) or discontinue their use (group B). Control subjects not under antithrombotic therapy will also be recruited (group C). The primary endpoint is gastrointestinal hemorrhage and the secondary endpoint is a cardiovascular event.

Summary : This is the first multicenter trial in Japan to investigate the safety of continuing antithrombotic therapy during EGD with biopsy. *Shinshu Med J 60 : 143—148, 2012*

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Key words : thrombosis, platelet inhibitors, aspirin, anticoagulants, endoscopic procedure

I Introduction

Evidence has accumulated to support the use of anticoagulants and antiplatelet agents for the prevention of cardio- and cerebrovascular diseases. The periprocedural management of patients who might require temporary interruption of these agents to undergo diagnostic and therapeutic endoscopy is a common clinical consideration. The decision is challenging because the risk of a thrombotic event during the interruption of therapy must be balanced carefully against the risk of bleeding when treatment is resumed.

In deciding whether to temporarily discontinue antithrombotics during a procedure, it is important to assess the inherent risk of bleeding associated with that specific procedure. The risk varies with procedure type and depends on whether or not therapeutic interventions are performed. It is generally accepted that all diagnostic procedures with or without mucosal biopsy, as well as endoscopic retro-

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grade cholangiopancreatography without sphincterotomy, diagnostic balloon-assisted enteroscopy, and endosonography without tissue sampling, are low-risk procedures[1]. Procedures with an increased risk of bleeding include endoscopic polypectomy or endoscopic mucosal resection, laser ablation, therapeutic balloon-assisted enteroscopy, and endoscopic sphincterotomy. These therapeutic procedures have the potential to cause bleeding that is inaccessible or uncontrollable by endoscopic means.

Clinical evidence suggests that the continued administration of warfarin during the periendoscopic period carries a low risk of bleeding in low-risk procedures[1]. In a retrospective study, Gerson et al. found that in 171 low-risk procedures (upper endoscopy and colonoscopy, including the use of mucosal biopsy) in patients taking therapeutic doses of warfarin, no bleeding was clinically evident[2].

Aspirin has been shown to prolong bleeding times to up to 48 hours after ingestion[3]. Two previous studies have demonstrated that aspirin is not associated with an increased risk of post-endoscopy bleeding[4][5]. Furthermore, current studies suggest that aspirin administration in the periendoscopic period is safe, even after high-risk endoscopic procedures such as polypectomy[4][6] or sphincterotomy[7].

Another antiplatelet agent, clopidogrel, causes irreversible platelet inhibition. Upon drug cessation, a minimum of 5 days is required for platelet aggregation to return to 50 % of normal. The published data do not provide an accurate gauge for determining the risk of bleeding associated with clopidogrel (or ticlopidine) after an endoscopic procedure. Current guidelines recommend withholding clopidogrel for at least 7 days before a high-risk endoscopic procedure[8]. Patients at high risk for a cardiovascular event, particularly stent thrombosis, should defer elective endoscopic procedures until clopidogrel can be safely discontinued[9].

In patients taking both aspirin and clopidogrel, the risk of bleeding after an endoscopic procedure has not been determined. However, the effects of this drug combination on the gastrointestinal tract have been studied. The combined use of 2 platelet antagonists significantly increases the risk of gastrointestinal bleeding when compared with monotherapy[10][11] and impairs the healing of ulcers[12]. The administration of clopidogrel in addition to aspirin increases the relative risk of gastrointestinal bleeding by up to 70 %[13]. Therefore, in patients who take clopidogrel plus aspirin, the bleeding risk will likely be reduced by stopping clopidogrel and continuing aspirin before an elective endoscopy.

In 2005, the Japan Gastroenterological Endoscopy Society (JGES) established Japanese guidelines for the management of anticoagulants and antiplatelet agents during endoscopic procedures[9]. According to this recommendation, patients at low risk for a thromboembolic event should discontinue the use of antithrombotics or anti-platelet agents before a low-risk procedure as follows : warfarin, 3-4 days ; aspirin, 3 days ; and ticlopidine, 5 days. The recommendations of the Japanese Circulation Society (2009) are similar to those of the JGES[14]. There are discrepancies between Japanese and American guidelines, even though the JGES guidelines were established using the American Society for Gastrointestinal Endoscopy (ASGE) guidelines as a reference. The recommendations for management for each category by a combination of procedural risks and thrombotic risks differ between ASGE and JGES. Specifically, the ASGE guidelines recommend that aspirin and warfarin be continued for endoscopic procedures with a low risk of inducing bleeding. This ASGE recommendation regarding continuing antithrombotic agents during the periendoscopic period is based on the clinical data about bleeding risk reported by Gerson[1] and on the fact that there are no clinical trials demonstrating an increased incidence of bleeding in patients who have undergone upper endoscopy with biopsy while taking antithrombotic agents. In contrast, the JGES guidelines recommend cessation of aspirin and warfarin before endoscopy, even if the procedure is classified as low risk. However the JGES guidelines have no Japanese epidemiologic data about gastrointestinal bleeding after biopsy procedure without discontinuation of antithrombotic agent as a reference. About

discontinuation of aspirin, the JGES guidelines refer to one report that bleeding time and bleeding volume were normalized 3 days after cessation in 11 healthy men[15]. In the case of warfarin, the guidelines do not mention the length of discontinuation with reference to the risk of bleeding. Racial differences in susceptibility to bleeding and manifestations of thromboembolism may lead to different recommendations by different countries[16].

On the other hand, Ono et al. performed a retrospective analysis of the management of anticoagulants and antiplatelet agents for scheduled endoscopy in Japanese patients. Among 8921 patients who underwent scheduled endoscopy, 1383 patients (15.5 %) were receiving anticoagulants or antiplatelet agents[17]. Of the 556 patients who underwent endoscopy without cessation of these medications, 41 (7.4 %) underwent invasive procedures, including endoscopic mucosal resection. No complications related to bleeding were observed in these patients.

Fujishiro et al.[18] performed a survey on the management of antithrombotic therapy for endoscopic procedures. Participants comprised 13 endoscopists from 13 hospitals in the Tokyo area. Three endoscopists (23 %) reported having patients who experienced thromboembolic events during the discontinuation of anticoagulants or antiplatelet agents for endoscopy. In contrast, no endoscopists reported having patients with severe bleeding due to continuation of antithrombotic therapy during esophagogastroduodenoscopy (EGD) with biopsy.

Thus the continued administration of antithrombotic agents during EGD with biopsy is quite likely to be acceptable also in Japan.

EGD is a common endoscopic procedure, and EGD with biopsy is considered to be a low-risk procedure by both Japanese and Western guidelines. If the procedure is classified as a low-risk procedure, then the risk of hemorrhage is low. The continued administration of antithrombotic agents during EGD with biopsy is thus acceptable by Western guidelines. In contrast, Japanese guidelines recommend stopping antithrombotic agents for a considerable amount of time, even when the endoscopic procedures are classified as low risk.

The actual risk of post-endoscopic bleeding associated with taking antithrombotic agents is unknown in Japanese patients. In this trial, we will investigate the feasibility of performing EGD with biopsy without the cessation of antithrombotic agents in Japanese patients, in accordance with the ASGE guidelines.

II Methods

A Objective

The Assessment of Safety of using Antithrombotic Agents during endoscopic procedures (ASAMA) study is a prospective, non-randomized, multicenter study to investigate the feasibility of continuing antithrombotic agents during EGD with biopsy.

B Study Population

Patients who will undergo scheduled EGD with or without biopsy and are receiving warfarin or antiplatelet agents [aspirin, thienopyridines (clopidogrel or ticlopidine)] will be candidates to be enrolled (Fig. 1). The patients will be divided into 2 groups, and will either continue antithrombotic agents (group A) or discontinue these agents (group B). All the patients will be informed of the risks and benefits of continuing or discontinuing antithrombotic agents. Patients will be divided into candidates for group A or B at their own request and written informed consent will be obtained. In group A, patients who normally take only 1 antithrombotic agent will continue taking their medication as usual. Those who are taking clopidogrel or ticlopidine in combination with aspirin will stop the clopidogrel or ticlopidine 7 days before the procedure. Patients who are taking both warfarin and an antiplatelet agent will discontinue the use of either 1 of the 2 drugs ; the drug to be discontinued will be chosen at the discretion of each patient's attending physician. These protocols of continuing antithrombotic agents in group A are in accordance with ASGE guidelines. In group B, antithrombotic agents will be discontinued according to the guidelines of

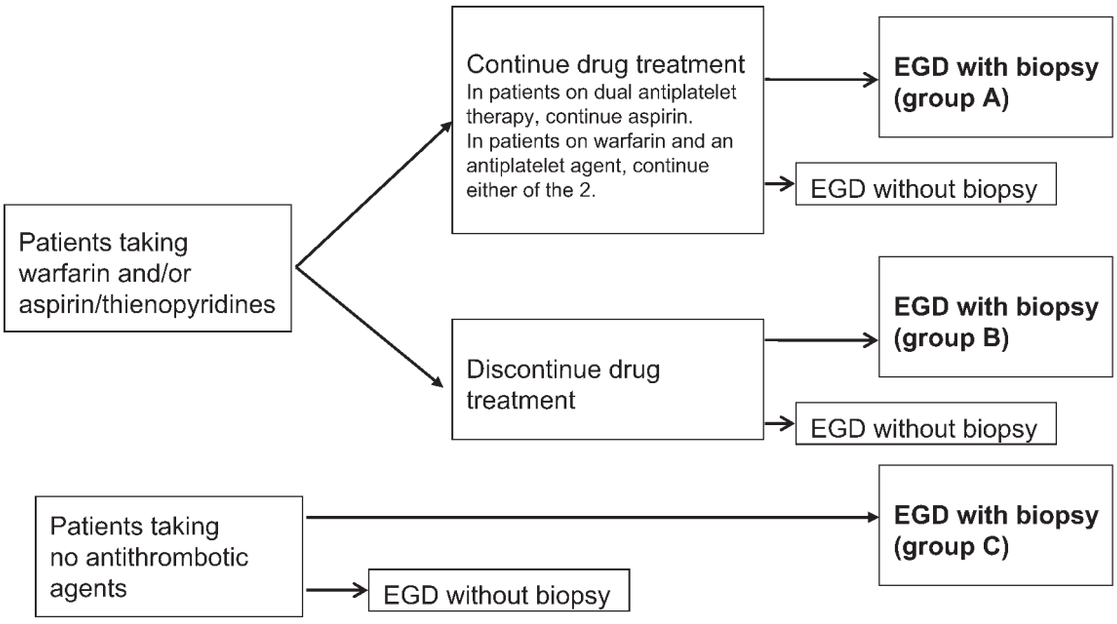

Fig. 1 ASAMA study design. EGD ; esophagogastroduodenoscopy

JGES. Patients not under antithrombotic therapy will also be candidates to be enrolled (group C). The decision whether to perform biopsy or not depends on the endoscopist. Among these candidates, the patients who receive biopsy at the time of EGD will be eventually enrolled in this study (Group A, B, or C). Patients with active gastrointestinal bleeding at the time of EGD before biopsy will be excluded from the study. Five hundred subjects will be enrolled in each group.

Other exclusion criteria include the use of antithrombotic agents other than aspirin and thienopyridines, the presence of drug-eluting stents implanted within 1 year of the EGD procedure, a poor international normalized ratio (INR＞3.0) within 1 month of the procedure, the presence of a bleeding disorder, and pregnancy. Patients will be recruited from 18 participating sites in Nagano prefecture in Japan and will be enrolled from March 2011 to March 2014.

The protocol has been reviewed and approved by each participating site's ethics committee. The trial has been registered at the University Hospital Medical Information Network (UMIN) (ID000004937).

C Study Endpoints

The primary endpoint is the occurrence of gastrointestinal hemorrhagic events requiring any treatment. The secondary endpoint is a cardiovascular event during the periprocedural period. The percentage of endpoints will be compared between the 3 groups.

Ⅲ Discussion

There is little consensus in our daily practice regarding the management of anticoagulation and antiplatelet therapy for endoscopic procedures, even after the establishment of the Japanese guidelines. The ASAMA study is the first prospective multicenter trial to investigate the safety of continuing antithrombotic agents during elective EGD with biopsy in Japanese patients.

This trial is non-randomized because today's JGES guidelines recommend the cessation of antithrombotic agents before endoscopy. All the patients will be enrolled into group A or B at their own request, after receiving information on the risks and benefits of continuing or discontinuing antithrombotic agents. If the frequency of gastrointestinal hemorrhagic events is identical among the three groups, a further randomized controlled trial will be needed.

This trial addresses an important issue, and its results could influence the treatment of many hundreds of thousands of patients under antithrombotic therapy.

Ⅳ Summary

This is the first multicenter trial in Japan to investigate the safety of continuing antithrombotic therapy during EGD with biopsy.

Ⅴ Appendix

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