Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel

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Background: Percutaneous endoscopic gastrostomy (PEG) is an invasive procedure that can result in bleeding. Guidelines recommend discontinuing clopidogrel for 7 to 10 days, but not withholding aspirin, before PEG. Serotonin reuptake inhibitors (SRIs) have been associated with an increased risk of GI bleeding.

Objective: To determine whether there is an association between periprocedural aspirin, clopidogrel, or SRI use and bleeding in patients who underwent PEG tube placement.

Design: Retrospective cohort study.

Setting: Large quaternary-care academic medical center.

Patients: A total of 990 patients (525 men) with a median age of 69.8 years who underwent PEG from January 1999 to April 2009.

Interventions: PEG tube placement.

Main Outcome Measurements: GI bleeding.

Results: Sixteen patients (1.6%) had evidence of bleeding during the first 48 hours after PEG, and 12 patients (1.2%) had evidence of bleeding between 48 hours and 14 days after PEG. Thirty-six patients (3.6%) received high-dose aspirin (>325 mg), 27 patients (2.7%) received clopidogrel (75 mg), and 99 patients (10%) received an SRI before PEG. Twenty-four patients (2.4%) received high-dose aspirin, 25 patients (2.5%) received clopidogrel, and 130 patients (13.1%) received an SRI after PEG. Multivariate analysis demonstrated no association between periprocedural use of aspirin (at any dose) or clopidogrel and post-PEG bleeding. However, SRIs administered 24 hours or less before PEG were associated with a significantly higher odds of post-PEG bleeding (adjusted odds ratio 4.1; 95% CI, 1.1-13.4; $P = .04$).

Limitations: Retrospective, single-center study with limited statistical power despite a relatively large cohort of patients.

Conclusions: Use of aspirin or clopidogrel before or after PEG was not associated with procedure-related bleeding. SRI use in the 24 hours before PEG was associated with an increased risk of bleeding. (Gastrointest Endosc 2011;74:22-34.)

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; H2RA, H_2-receptor antagonist; ICU, intensive care unit; NNTH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; PPB, post-PEG bleeding; PPI, proton pump inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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Percutaneous endoscopic gastrostomy (PEG) is classified as a higher risk procedure, and bleeding is a recognized adverse event that can occur after PEG.[1] The reported rate of bleeding after PEG is approximately 2.5%.[2,3] Gastroenterologists and surgeons are commonly asked to perform PEGs in patients taking aspirin and/or other antithrombotic agents, such as clopidogrel (Plavix; Sanofi-Aventis, Bridgewater, NJ), because these medications are frequently used for primary and secondary cardiovascular and cerebrovascular prophylaxis[4-8] and in the setting of cardiovascular stenting.[9] Aspirin alone in doses as low as 75 mg/day has been shown to increase the risk of spontaneous upper GI bleeding by two- to threefold.[10-12] The risk of upper GI bleeding is similarly increased in patients taking clopidogrel.[13] However, the risk of bleeding after PEG in patients receiving antithrombotic therapy remains undetermined.

Serotonin reuptake inhibitors (SRIs) are commonly prescribed medications that are used to treat a number of psychiatric conditions.[14-17] Because of their efficacy and generally mild side-effect profile, SRI use continues to increase.[18,19] Recent retrospective and observational studies have suggested a relationship between SRI use and GI bleeding.[20-29] Case reports have also noted various bleeding complications in SRI users ranging from ecchymoses and epistaxis[30,31] to more serious conditions such as genitourinary bleeding,[32] retroperitoneal hematoma,[33] intracranial bleeding,[34] and bleeding after orthopedic procedures.[35,36] The increased risk of bleeding associated with SRIs has been attributed to impaired platelet function as a result of the inhibition of serotonin uptake. Platelets cannot synthesize serotonin, which must be taken up from the circulation by transporters. Because serotonin plays an integral role in the promotion of platelet aggregation, inhibiting the uptake of serotonin by platelets impairs their normal homeostatic mechanisms.[37-39] Studies have also suggested a possible synergistic effect between SRIs and aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs),[20,22,26,28,29,40] which might lead to an even greater increased risk of bleeding.

Despite these associations between antiplatelet therapies and bleeding, guidelines published separately by the American Society for Gastrointestinal Endoscopy (ASGE)[41] and American College of Cardiology Foundation Task Force[42] have suggested that aspirin therapy, in general, should be continued for essential endoscopic procedures in patients at risk of thromboembolic events. These guidelines are less clear regarding the use of clopidogrel in patients at risk of thromboembolic events who require endoscopic interventions, and they do not make any recommendation regarding the use of SRIs in these patients. The aim of our study was to determine whether there is an increased risk of postprocedure bleeding in patients exposed to aspirin, clopidogrel, or SRIs up to 72 hours before or 48 hours after PEG.

Take-home Message

- Aspirin (of any dose) or clopidogrel administered within 72 hours before or 48 hours after PEG was not associated with an increased risk of postprocedure bleeding.
- Serotonin reuptake inhibitors (SRIs) administered during the 24 hours before PEG were associated with a 4-times increased odds of postprocedure bleeding. As such, withholding SRIs 24 hours before PEG might reduce the risk of postprocedure bleeding.

METHODS

We conducted a retrospective, single-center cohort study that included inpatients at the University of Virginia Hospital, which is a large quaternary-care center. Patients on the neurology and cardiothoracic services who underwent PEG from January 1999 to April 2009 were included. Patients were limited to the neurology and cardiothoracic services because they were more likely to require and be exposed to aspirin and/or clopidogrel before and after PEG. This study was approved by our institutional review board.

Patients were identified by using a hospital database. The electronic medical records (including progress notes, discharge summaries, medication logs, laboratory values, endoscopy reports, and transfusion records) were systematically reviewed by 2 independent study personnel. A third investigator subsequently reviewed all cases and confirmed the findings of the 2 reviewers, including medication exposures. PEG was performed by using the standard push or pull technique adapted from the method as first described by Ponsky and Gauderer.[43] Patients who had a history of a bleeding diathesis, coagulopathy, Mallory-Weiss syndrome, esophagogastric varices, or upper GI bleed within the previous 6 months were excluded from the study.

Definition of SRIs

Antidepressants were classified based on their inhibitory action of the serotonin reuptake mechanism: (1) selective serotonin reuptake inhibitors (SSRIs) included sertraline hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, citalopram hydrobromide, and escitalopram oxalate and (2) selective serotonin and norepinephrine reuptake inhibitors (SNRIs) included venlafaxine and duloxetine hydrochloride.[20] For some analyses, SSRIs and SNRIs were combined in a single category, SRIs.

Definition of medication exposure

Data were retrieved on the use of the following drugs administered within 48 or 72 hours before or after PEG: SSRIs, SNRIs, aspirin, clopidogrel, NSAIDs, warfarin, heparin, low molecular weight heparin, proton pump inhibi-