CRITICAL CARE

How soon to start: aspirin resumption after upper gastrointestinal bleed?

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Extended abstract

Citation
Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong VW, Chan FK. Ann Intern Med. 2010 Jan 5;152(1):1-9. Epub 2009 Nov 30.

Background
It is uncertain whether aspirin therapy should be continued after endoscopic hemostatic therapy in patients who develop peptic ulcer bleeding while receiving low-dose aspirin.

Objective
To test that continuing aspirin therapy with proton-pump inhibitors after endoscopic control of ulcer bleeding was not inferior to stopping aspirin therapy, in terms of recurrent ulcer bleeding in adults with cardiovascular or cerebrovascular diseases.

Design
A parallel randomized, placebo-controlled noninferiority trial, in which both patients and clinicians were blinded to treatment assignment, was conducted from 2003 to 2006 by using computer-generated numbers in concealed envelopes. (ClinicalTrials.gov registration number: NCT00153725)

Setting
A tertiary endoscopy center.

Patients
Low-dose aspirin recipients with peptic ulcer bleeding.

Intervention
78 patients received aspirin, 80 mg/d, and 78 received placebo for 8 weeks immediately after endoscopic therapy. All patients received a 72-hour infusion of pantoprazole followed by oral pantoprazole. All patients completed follow-up.

Measurements
The primary end point was recurrent ulcer bleeding within 30 days confirmed by endoscopy. Secondary end points were all-cause and cause-specific mortality in 8 weeks.

Results
156 patients were included in an intention-to-treat analysis. Three patients withdrew from the trial before finishing follow-up. Recurrent ulcer bleeding within 30 days was 10.3% in the aspirin group and 5.4% in the placebo group (difference, 4.9 percentage points [95% CI, −3.6 to 13.4 percentage points]). Patients who received aspirin had lower all-cause mortality rates than patients who received placebo (1.3% vs. 12.9%; difference, 11.6 percentage points [CI, 3.7 to 19.5 percentage points]). Patients in the aspirin group had lower mortality rates attributable to cardiovascular, cerebrovascular, or gastrointestinal complications than patients in the placebo group (1.3% vs. 10.3%; difference, 9 percentage points [CI, 1.7 to 16.3 percentage points]).

Limitations
The sample size is relatively small, and only low-dose aspirin, 80 mg, was used. Two patients with recurrent bleeding in the placebo group did not have further endoscopy.

Conclusion
Among low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding but potentially reduces mortality rates. Larger trials are needed to confirm these findings.

Commentary
Fifty million Americans use low-dose aspirin, 325mg/day or less, regularly for cardioprophylaxis[1]. The estimated

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average excess risk of upper gastrointestinal bleeding (UGIB) related to cardioprophylactic doses of ASA is 5 cases per 1000 ASA users per year[2]. Currently the 2010 International Consensus on Non-variceal Upper Gastrointestinal Bleeding is that - *In patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding.*[3] One significant problem with this recommendation is that the risks of when one outweighs the other is very ill defined. It has been shown that prolonged discontinuation of ASA therapy increases thrombotic risk[4]. This creates a conundrum for physicians trying to balance the risk of re-bleed vs. cardiac or cerebrovascular event risk.

The purpose of this study was to determine that restarting ASA therapy after endoscopic control of the UGIB was not inferior to stopping ASA therapy. It was a randomized placebo non-inferiority study where patients were randomly assigned to placebo or ASA therapy after endoscopic control of an UGIB. The primary outcome was to evaluate the occurrence of recurrent peptic ulcer bleed within 30 days of the initial event. Secondary outcomes included all cause mortality, and death attributed to cardiovascular, cerebrovascular or gastrointestinal complications. Secondary endpoints included blood transfusion requirement, duration of hospital stay, requirement of surgery, and recurrence of acute ischemic events (ACS/CVA). There was no significant difference in the primary outcome measure, incidence of recurrent ulcer bleeding at 30 days (10.3% in the low-dose aspirin group and 5.4% in the placebo group, difference 4.9 percentage points, [CI -3.6 to 13.4 percentage points]). All cause mortality was lower in the ASA group (1.3% in the ASA group at 56 days and 12.9% in the placebo group, difference of 11.6 percentage points, [CI 3.7 to 19.5 percentage points]). There was no difference between the two groups regarding the other secondary outcomes.

The strength of this paper is that it was a well designed study. The patients were well randomized and the evaluators were blinded to the treatment groups. Limitations include a small sample size and concerns as to whether the information can be extrapolated to patients that use higher doses of ASA. In addition, there were 2 patients in the placebo group that did not undergo endoscopy -1 died before getting to the hospital, and the other patient was too unstable for recurrent endoscopy. These two patients were not added to the primary analyses. If they were added to the cases of recurrent bleeding the difference between the two groups would be reduced.

The findings of this study suggest that early resumption of ASA has a trade-off. While early resumption increased risk of re-bleeding, it reduced risk of subsequent cardiovascular events. This study used a single primary endpoint and non-inferiority margin of 10%, i.e. the trial had adequate power to detect a >10% higher risk of re-bleeding in the group where ASA was resumed immediately. For instance, the re-bleeding risk in the group where ASA was resumed immediately was 4.9% higher compared to the group in whom ASA was resumed later. This difference was not statistically significant, but the study was underpowered to detect such small differences. These findings raise questions regarding the optimal design of trials to address this issue. Is the 10% non-inferiority margin acceptable and should the authors have designed a study to detect smaller differences in re-bleeding risk? Similar to prior studies,[5] one approach would be to use a non-inferiority design to compare bleeding risk and superiority design to compare all-cause mortality.

The results of this study need to be confirmed in a larger study as its treatment implications for all health providers could be great in terms of managing their patients after UGI bleeds. Like any good study, it raises several additional questions: What is the appropriate dose of ASA that should be restarted? What is the appropriate time interval from endoscopy until ASA resumption?

Recommendation

In conclusion, patients that have an UGIB that need cardioprophylaxis or cerebrovascular prophylaxis should be restarted on their ASA therapy as soon as endoscopic control of their UGIB source has been controlled.

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