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Recommencing aspirin following a peptic ulcer bleed: when is the time right?

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Title: Recommencing continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial
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Summary

As the population ages it is increasingly common for patients who present with a peptic ulcer bleed to have concomitant cerebrovascular or cardiovascular disease. Traditionally antiplatelet therapy, including aspirin, is stopped for a period of 4-8 weeks following an acute bleed although this approach is not evidence based. A study by Sung et al [1] addressed the issue of what to do with aspirin prescription in this scenario with a single-center double-blind parallel randomized placebo-controlled trial. To be included in the study, participants had to be taking up to 325 mg of aspirin per day for secondary prophylaxis and present with an upper gastrointestinal (GI) bleed. The study required endoscopic findings of a peptic ulcer with active bleeding or stigmata of recent hemorrhage (visible vessel or adherent clot). All participants received dual endoscopic therapy with adrenaline and heater probe to achieve hemostasis. Participants were then commenced on a 72-hour continuous intravenous infusion of proton pump inhibitor (PPI) and randomized to either aspirin (80 mg/day) or placebo for 8 weeks. Both groups received oral PPI (pantoprazole 40mg/day) for the duration of the study. The primary endpoint of the study was recurrent peptic ulcer bleeding within 30 days of the index endoscopy. The study recruited 156 participants (78 in each arm) and was powered as a non-inferiority study to detect a 10% difference in recurrent peptic ulcer bleeding rates at 30 days.

The results demonstrated a recurrent bleed rate of 10.3% (95% CI 3.4 - 17.2) in the aspirin group compared with 5.4% (95% CI 0.3 - 10.5) in the placebo group (a difference of 4.9 percentage points (95% CI -3.6 - 13.4) at 30 days. The authors therefore concluded that continuing aspirin was not equal to stopping aspirin therapy in terms of the risk of a recurrent ulcer bleed.

Regarding the secondary endpoints of the study there was no significant difference in the amount of blood transfused or hospital stay between each arm of the study. However there was a significant difference in mortality between groups at 8 weeks: 1.3% in the aspirin group (1 patient died of congestive cardiac failure) vs. 12.9% in the placebo group (including 5 participants who died of vascular complications including myocardial infarction and stroke; 2 who died of perforated ulcer and 1 who died of uncontrolled bleeding); p=0.005. The difference in mortality remained significant when deaths only due to cardiovascular, cerebrovascular and gastrointestinal causes were included.

Opinion

It is well recognized that patients with significant co-morbidities, such as cardiovascular disease, have an increased mortality when presenting with a GI bleed. Indeed, this has been recognized in widely used prognostic scoring systems such as Rockall and Blatchford [2,3].

The study by Sung et al [1] demonstrated a significant increase in mortality when the patient on long-term aspirin had this withheld for 8 weeks following presentation with a peptic ulcer bleed, as is common practice. The difference between groups was striking (1.3% vs.12.9% at 8 weeks). Although the authors were unable to conclude that there was not an increased incidence of recurrent ulcer bleeding in the group treated with aspirin, the majority of recurrent bleeds were within the first 5 days post-endoscopy and were not associated with increased hospital stay or blood transfusion requirements.

This study reminds us that the majority of deaths from peptic ulcer bleed are not as direct complications of the ulcers themselves. This has been found in other studies [4,5], but is a timely reminder to the gastroenterologist to be holistic in their approach to patients with ulcer bleeds and pay particular attention to the chest (for sepsis or fluid overload), heart and

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renal function. We would suggest that elderly patients with multiple co-morbidities should have a more prolonged hospital stay with close monitoring of these organ systems. We generally discharge this group of patients after 5-7 days inpatient stay.

Following the publication of the Sung paper, and on consideration of its findings, our clinical practice has changed. In patients requiring aspirin for secondary prophylaxis of significant cerebrovascular or cardiovascular disease we would consider restarting aspirin at 3 days post endoscopy (i.e., once IV PPI infusion has stopped) and then monitor patients for at least a further 48 hours prior to discharge. In these cases we have a low threshold for repeat endoscopy prior to discharge in order to assess ulcer healing. We also recommend vigilance regarding *Helicobacter pylori* diagnosis, eradication and confirmation of eradication with a subsequent breath test six weeks to three months later in patients who require lifelong aspirin therapy. In such patients on aspirin, PPIs should also be co-prescribed long term.

The limitations of this study, however, must not be overlooked. Whilst the most striking outcome is the mortality data, the study was not powered to this endpoint and there is the possibility of a type 1 error. Moreover, the design of the study was unusual in that it was powered as a non-inferiority study to detect a difference in recurrent GI bleeding.

The study also does not address the issue of other anticoagulants or antiplatelets such as warfarin or clopidogrel (indeed the one patient on clopidogrel had it stopped as part of the study design) or of the patient who has recently received a drug-eluting coronary stent who is at high risk of thrombosis should clopidogrel be stopped. We would suggest that in these scenarios in particular, there is a role for second-look endoscopy as there is some evidence that a second look endoscopy with heater probe as endoscopic therapy reduces recurrent bleeding from peptic ulcers [6]. As previously mentioned and if there is significant concern about certain patients who bled from large excavating ulcers or denuded vessels, assessment of ulcer healing prior to discharge from hospital makes sense.

Notwithstanding the limitations and caveats discussed, this remains an important and intriguing study as it highlights the clinical judgement required to balance the risks of recurrent ulcer bleeding (which whilst this seems logical, is also relatively simple to intervene and available evidence would suggest tends to be non clinically significant) against the benefits of reduced vascular events (which while the risks are perhaps relatively esoteric to the gastroenterologist, intervention post hoc is more challenging). Although further studies are needed Sung et al challenge conventional thinking, have altered our clinical practice, and once again remind us to be holistic in our approach to GI bleeding.

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