Should we give a PPI IV before endoscopy in patients with upper GI bleeding?

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The rationale for acid suppression therapy in upper gastrointestinal (GI) bleeding is based on the deleterious effects of acid on clot formation and stability as shown by *in vivo* and animal studies [1]. A Cochrane Collaboration meta-analysis of randomized controlled trials (RCTs) has shown that proton pump inhibitor (PPI) treatment, compared to treatment with a histamine-2 receptor antagonist (H_2RA) or placebo, initiated after endoscopy in patients with peptic ulcer bleeding reduced re-bleeding and the need for surgery and repeated endoscopic hemostatic treatment [2]. Post-endoscopic PPI treatment also improved mortality among patients with ulcers demonstrating high-risk endoscopic stigmata (active bleeding or non-bleeding visible vessel). When the meta-analysis was restricted to trials that had been conducted in Asia, post-endoscopic PPI treatment reduced mortality regardless of the severity of baseline endoscopic stigmata [2,3].

Given the above evidence and the knowledge that peptic ulcer disease is the principal cause of upper GI bleeding, it is not surprising that PPI treatment is often used in clinical practice for patients with upper GI bleeding before endoscopic confirmation of the cause of the bleed [4]. However, this practice represents a major challenge for formularies, especially since the relevant evidence has not been robust. Guidelines from a multi-society consensus group statement recommend the use of empirical high-dose IV PPI treatment in patients with upper GI bleeding waiting for endoscopy, although only 40% of the consensus panel agreed to this recommendation without any reservations [5].

The recently published study by Dr. James Lau and colleagues from Hong Kong provides further evidence on this controversial issue [6]. This was a double-blind RCT of high methodological quality, conducted by a world-leading team in peptic ulcer research. This study showed that, compared to placebo, high-dose continuous IV infusion of omeprazole before endoscopy in patients with upper GI bleeding significantly reduced the severity of endoscopic signs of recent bleeding, the need for endoscopic therapy and the length of hospital stay. There was no evidence of an effect on recurrent bleeding, blood transfusions, need for surgery or mortality.

In general, these findings are in agreement with the results of a Cochrane Collaboration meta-analysis of five RCTs that was published in 2006 [7]. At that time only the preliminary results of the study by Lau et al. had been available. The meta-analysis found no evidence that pre-endoscopic treatment with a PPI, compared to an H_2RA or placebo, affected clinically important outcomes including mortality, re-bleeding, need for surgery and need for endoscopic hemostatic treatment. The lack of effect on endoscopic hemostatic treatment requirements was the only divergence from the finding of the trial by Lau et al.. The meta-analysis also showed that pre-endoscopic PPI treatment significantly reduced the proportion of patients with endoscopic signs of recent bleeding (active bleeding, non-bleeding visible vessel or adherent clot) at index endoscopy; pooled rates were 37.2% on PPI treatment and 46.5% on control treatment (OR: 0.67; 95% CI: 0.54 to 0.84). Although the formal update of the meta-analysis is not due before 2008, a close look at the forest plots suggests that the main pooled results are unlikely to change significantly when the final results of the study by Lau et al. [6] will be included. Of note, among the studies included in the meta-analysis, the study by Lau et al. [6] was the only one that had used a high-dose of IV PPI.

What is the clinical significance of the findings of the recent Hong Kong study? From one point of view, this study failed to demonstrate that pre-endoscopic use of a PPI in patients with upper GI bleeding affected mortality or recurrent bleeding, which are the most important clinical outcomes [6].

However, it is not clear if the glass is half full or half empty. From another point of view, Lau and colleagues have proved that IV omeprazole before endoscopy significantly reduced the need for endoscopic hemostatic treatment at index endoscopy [6]. This alone may be sufficient to justify empirical use of PPI before endoscopy for patients with upper GI bleeding, even without evidence of a beneficial effect on mortality and re-bleeding. Furthermore, one has to admit that it would have been extremely difficult to detect a significant treatment effect on mortality or recurrent bleeding; any treatment effect of pre-endoscopic PPIs would have been diluted by the highly-effective treatment (endoscopic hemostatic treatment and high-dose infusion of omeprazole) that both treatment groups rece-

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ived by the morning following admission. (The mean duration of infusion prior to endoscopy was 15 hours only). The sample size of the current study was estimated *a priori* according to the primary outcome, i.e. the need for endoscopic treatment. It would have been impractical to conduct a RCT aiming to demonstrate an effect of pre-endoscopic PPI treatment on mortality, as this would have required a sample size of several thousand patients.

The reduced need for endoscopic treatment may translate into increased cost-effectiveness. In fact, even prior to the publication of the study by Lau and colleagues, cost-effectiveness studies had suggested that pre-endoscopic administration of PPIs in upper GI bleeding is cost-effective in the USA [8], Canada [9] and the UK [10].

However, there are some concerns regarding the applicability of the findings of the Hong Kong study to European patient populations. It has been shown that PPI treatment for peptic ulcer bleeding is more efficacious in studies conducted in Asia compared to studies conducted in Europe or North America. Likely explanations for this are the lower parietal cell mass, the higher prevalence of *H. pylori* infection and the higher likelihood of genetically-determined slow metabolism of PPIs among Asian patients [3].

Furthermore, the findings of the Hong Kong study may not be applicable to geographic areas with a lower proportion of patients with peptic ulcer bleeding among those presenting with upper GI bleeding. Peptic ulcer is the source of bleeding in 60% of patients with upper GI bleeding in Hong Kong [6], but the relative frequency of peptic ulcer bleeding may be lower in Europe and North America. This is an important consideration since the beneficial effect seen in the study by Lau et al. on the requirements for endoscopic therapy was confined to patients with bleeding from peptic ulcers; as expected, there was no difference in the need for endoscopic therapy among patients with other sources of bleeding. The percentage of patients with peptic ulcer bleeding among upper GI bleeds in two UK RCTs that assessed pre-endoscopic use of PPIs was only 43% [11,12].

With regard to Poland, it is worth mentioning the RCT reported by Wallner et al. from Lublin in 1996 [13]. In this study, IV omeprazole was found to be superior to IV ranitidine in patients with upper GI bleeding. By excluding patients with hepatic insufficiency, Wallner and colleagues managed to include a high proportion of patients with peptic ulcer bleeding (75%). However, they had chosen a rather subjective primary outcome, namely the time required for regression of clinical signs of fresh upper GI bleeding, confirmed by endoscopy. Given that the study was not blinded, and that the exact definition of clinical signs of fresh upper GI bleeding was not stated, the assessment of the primary outcome could have been prone to bias. Apparently, no endoscopic haemostatic treatment was offered; this may explain the relatively long time intervals required for regression of bleeding (mean time of 3.2 days for the omeprazole group and 6 days for the ranitidine group) [13].

Obviously, there is a need for further high-quality RCTs to evaluate the efficacy of high-dose IV PPI treatment before endoscopy in European patients with upper GI bleeding. Cost-effectiveness studies for each national heath care system are also needed.

Meanwhile, taking the current evidence into consideration, should we give omeprazole (or another PPI) IV before endoscopy in patients with upper GI bleeding? The answer is probably yes, although the evidence is not strong. Until new consensus guidelines are published, it seems reasonable for clinicians to initiate high-dose IV PPI treatment to patients with signs of upper GI bleeding while waiting for endoscopy. This can be considered a "low risk" intervention that may produce some benefit. It should be emphasized though, that PPI treatment is not a substitute for prompt fluid resuscitation and appropriate diagnostic and, where necessary, therapeutics endoscopy. After endoscopy, PPI treatment should only be continued in those patients who were found to have bled from peptic ulcer disease.

From the Editor

Synopsis: Lau JY, Leung WK, Wu JC, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007; 356: 1631-1640

In this randomized controlled trial of 631 patients with upper gastrointestinal bleeding it has been shown that preemptive infusion of omeprazole before endoscopy (80 mg i.v. bolus injection and then infusion 8 mg per hour) compared to placebo resulted in the lower need for endoscopic treatment in the whole population (RRR: 33%, 95% CI: 10–49; NNT: 11, 95% CI: 7–38) and in the subgroup of patients with peptic ulcer (RRR: 39%, 95% CI: 16–56; NNT: 9, 95% CI: 6–29) and shortened the duration of hospital stay. On endoscopy, fewer patients in the omeprazole group had actively bleeding ulcers and more had ulcers with clean bases. There were no significant differences between both groups in the number of patients who had recurrent bleeding and who needed urgent endoscopy. In patients with peptic ulcers omeprazole did not decrease the need for emergency surgery.

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