Therapeutics

Review: In high-risk ulcers, intermittent and continuous PPI therapy do not differ for recurrent bleeding

Clinical impact ratings: ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆ ★★★★★☆

Question
In patients with high-risk bleeding ulcers, what is the efficacy of intermittent proton-pump inhibitor (PPI) therapy compared with bolus plus continuous-infusion PPI therapy?

Review scope
Included studies compared intermittent boluses of PPIs (any dose, frequency, or route) with IV PPI bolus (80 mg) followed by continuous infusion (8 mg/h for 72 h) in patients with upper gastrointestinal bleeding who were found to have a gastric or duodenal ulcer with active bleeding, a nonbleeding visible vessel, or an adherent clot; and had successful endoscopic hemostatic therapy. Ulcers with flat spots and clean bases were excluded. Primary outcome was recurrent bleeding within 7 days. Other outcomes included recurrent bleeding at 3 days and 30 days, and mortality.

Review methods
MEDLINE, EMBASE/Excerpta Medica, and Cochrane Central Register of Controlled Trials (all to Dec 2013), reference lists, and major gastroenterology conference proceedings (2009 to 2013) were searched for randomized controlled trials (RCTs). 13 RCTs (n = 1733) met selection criteria. 8 RCTs had adequate randomization; 1 had adequate allocation concealment; 5 had blinding of patients, personnel, and outcome assessors; and 12 had adequate follow-up. The primary analysis assessed noninferiority in the per-protocol population, with an absolute risk reduction of 3% as the margin of noninferiority.

Main results
Intermittent PPIs were noninferior to bolus plus continuous PPIs for recurrent bleeding at 7 days, 3 days, and 30 days (Table); and mortality. Groups did not differ for recurrent bleeding using standard analyses (Table).

Conclusion
In patients with high-risk bleeding ulcers, intermittent proton-pump inhibitor (PPI) therapy does not differ from bolus plus continuous-infusion PPI therapy for recurrent bleeding.

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Intermittent proton-pump inhibitors (PPIs) vs bolus plus continuous-infusion PPIs in patients with high-risk bleeding ulcers

<table>
<thead>
<tr>
<th>Recurrent bleeding</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>ARD (upper 95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intermittent PPI</td>
<td>Bolus +</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>continuous</td>
<td></td>
</tr>
<tr>
<td>At 7 d</td>
<td>10 (1373)</td>
<td>6.9%</td>
<td>9.4%</td>
<td>26% (−6 to 48)</td>
</tr>
<tr>
<td>At 3 d</td>
<td>9 (1173)</td>
<td>8.1%</td>
<td>11%</td>
<td>23% (−10 to 46)</td>
</tr>
<tr>
<td>At 30 d</td>
<td>13 (1733)</td>
<td>7.9%</td>
<td>8.7%</td>
<td>9% (−24 to 33)</td>
</tr>
</tbody>
</table>

*ARD = absolute risk difference; other abbreviations defined in Glossary. Weighted event rates, RRR, and CI calculated from control event rates and risk ratios for the intention-to-treat population in article using a fixed-effect model.
†Intermittent PPIs were noninferior (upper boundary of the 95% CI for the ARD was < 3% at each time point). Analysis was per protocol.

Commentary
Hemodynamically stable patients without serious comorbid conditions who have low-risk ulcers (e.g., clean-based, flat, pigmented spots) on endoscopy can be discharged on once-daily oral PPIs (1). In contrast, patients with bleeding from upper gastrointestinal tract ulceration and evidence of high-risk stigmata after successful endoscopic hemostasis benefit from high-dose parenteral PPI therapy (i.e., bolus followed by continuous-infusion PPIs for 72 h) (1). Meta-analyses of RCTs of high-dose PPI therapy have shown reductions in further bleeding, surgery, and mortality compared with endoscopic therapy alone (2, 3).

The recommendation for high-dose continuous infusion PPIs is based on the hypothesis that maintaining intraesophageal pH > 6 maximizes clot stabilization and prevents recurrent ulcer bleeding (4). The unresolved question is whether intermittent PPIs are an acceptable alternative to continuous-infusion PPIs. RCTs comparing intermittent and bolus plus continuous-infusion PPI therapy have been limited by small sample sizes, and prior meta-analyses have been inconclusive due to methodologic issues of including patients without high-risk stigmata or who did not have endoscopic therapy, and comparisons of high- vs low-dose PPIs rather than continuous vs intermittent infusion.

Several trials addressing these issues have since been reported and are included in the review by Sachar and colleagues of treatment for high-risk ulcer bleeding. The review found that intermittent PPI therapy was noninferior to bolus plus continuous-infusion PPI therapy for recurrent bleeding within 7 days, 3 days, and 30 days; need for surgery or urgent interventions; blood transfusions; length of stay; and mortality. Although overall recurrent bleeding rates were low in all studies, the meta-analysis supports the use of intermittent PPI therapy for high-risk ulcer bleeding as an alternative to bolus plus continuous-infusion PPI dosing, which is more costly and resource-intensive. It’s time for future guidelines to reflect this treatment option.

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References