Comparing intravenous and oral proton pump inhibitor therapy for bleeding peptic ulcers following endoscopic management: a systematic review and meta-analysis.

Background and Overview

Background
- Acute upper gastrointestinal (UGI) bleed is a common medical problem worldwide, and is associated with significant morbidity and mortality.
- Following the initial control of an active bleed, the focus of care shifts to the prevention of re-bleeding.
- One of the methods of preventing re-bleeding is controlling gastric pH.
  - Gastric acid promotes platelet degradation and fibrinolysis
  - Gastric pH <6 inhibits platelet aggregation, and <5 inhibits plasma coagulation
  - Thus, preventing gastric acid production consolidates clot formation and reduces the risk for re-bleeding.
- Proton pump inhibitors (PPIs) increase the gastric pH by inhibiting the H⁺/K⁺ ATPase proton pump, leading to suppression of acid secretion.
- Overuse of intravenous (IV) PPIs in UGI bleeding is common worldwide.
- Stigmata associated with re-bleeding include:
  - Major stigmata
    - Spurting, oozing vessels
    - Non-bleeding, visible vessels
    - Fresh, adherent clots
  - Other stigmata
    - Clean ulcer base
    - Flat spots
    - Any adherent clot
- Current guidelines recommend IV administration of PPIs initially for patients who are likely to re-bleed.
- This recommendation has come into question as studies have shown similarities in outcomes for oral (PO) and IV administration of PPIs in the prevention of UGI bleed.
  - These findings have led some recent guidelines to state that a specific route of administration cannot be recommended over the other
- A previous meta-analysis found similar outcomes for both routes of administration, but its utility was limited by a heterogenous sample population.

Objective
To compare PO and IV PPIs in patients with bleeding peptic ulcers after endoscopic management

Methods

Eligibility
- Type of study
  - Randomized control trials comparing PO vs IV PPIs
- Types of participants
  - Patients with symptoms of bleeding peptic ulcers undergoing endoscopic therapy to control bleeding
- Types of intervention
  - Comparing clinical outcomes after PO and IV PPIs after endoscopic treatment
- Outcomes
  - Primary
    - Recurrent bleeding
  - Secondary
    - Need for surgery
    - 30-day mortality
    - Need for a second endoscopic treatment
    - Need for a blood transfusion
    - Length of hospital stay
- Exclusions
  - Bleeding form UGI neoplasms
  - Already on PPI treatment

Statistical Analysis
- Odds ratios used to analyze dichotomous data (recurrent bleeding, need for surgery or second endoscopic treatment, and 30-day mortality)
- Mean difference used to calculate continuous variables (hospital stay and volume of blood transfused)
- Analysis of heterogeneity
  - $I^2$ statistic used to confirm and quantify the presence of inconsistency (heterogeneity significant if $I^2 > 50\%$)
Sensitivity analysis performed by removing each trial analysis in turn to determine the effect on the outcomes
Subgroup analysis compared the following factors:
- High-dose vs. non-high-dose IV PPIs
- High-dose oral vs. high-dose IV PPIs
- Patients with high-risk stigmata and recurrent bleeding at 15 and 30 days

### Results

<table>
<thead>
<tr>
<th>Trial Characteristics</th>
<th>9 trials, with 1,036 total participants, met inclusion criteria</th>
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<tbody>
<tr>
<td>Mean age of participants was 60 years</td>
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<td>71.1% were male</td>
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<td>Trial patients showed wide range of bleeding stigmata</td>
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<td>High-risk made up 65% in the PO group and 80% in the IV group</td>
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### Outcomes

- No significant differences concerning recurrent bleeding between PO and IV PPIs
  - OR 0.93, 95% CI 0.61, 1.46; P=0.77
- Secondary Outcomes
  - No significant difference in:
    - Need for a second endoscopic treatment
      - OR 0.69, 95% CI 0.39, 1.21; P=0.19
    - Need for surgical intervention
      - OR 0.77, 95% CI 0.25, 2.40; P=0.65
    - 30-day mortality
      - OR 0.89, 95% CI 0.27, 2.93; P=0.84
    - Mean number of transfusions
      - MD -0.03 units, 95% CI -0.26, 0.19 units; P=0.76
    - Length of hospital stay
      - MD -0.61 days, 95% CI -1.45, 0.23 days; P=0.16
    - Heterogeneity was found between studies in this endpoint, but this was based on the results of one study

### Conclusions and Discussion

- PO PPIs found to be equally effective to IV PPIs in regard to risk of recurrent bleeding, need for blood transfusion, need for repeated endoscopy, length of hospital stay, need for surgery, and overall mortality
- Subgroup analysis showed that high-dose IV PPIs were equivalent to low-dose PPIs for all outcomes considered.
  - High-dose PO PPIs vs high-dose IV PPIs were different only in need for blood transfusion (favored PO)
- PO and IV PPIs display equal efficacy in maintaining intragastric pH > 6 over 24 hours
- Limitations
  - Studies included were not powered for non-inferiority and place this meta-analysis at risk for a type 2 error
  - Not all trials met exact inclusion criteria
  - Trials examined different PPIs, which may limit generalizability
  - Most trials were conducted in Asian patients, who tend to be more efficient metabolizers of PPIs than Caucasians

### Application

- This study adds further strength to the argument that PO PPIs may be just as effective as IV PPIs when both routes are feasible.
- However, due to the small sample sizes included in the trials, it is unlikely that this publication produces any large-scale changes in prescribing patterns
- It is reasonable to recommend use of PO PPIs in patients with fewer stigmata associated with higher risk of re-bleeding
- The subgroup analysis suggesting equivalent outcomes between high- and low-doses is worth further exploration

### References