Intravenous proton pump inhibitors before endoscopy in bleeding peptic ulcer with high-risk stigmata: A multicentre comparative study

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BACKGROUND: It is not clear if starting intravenous proton pump inhibitors (IV PPI) before endoscopic therapy provides additional benefit over starting it afterward in patients with high-risk ulcer stigmata of peptic ulcer disease.

METHODS: All patients who received IV pantoprazole bolus and infusion and underwent endoscopy in six Canadian hospitals over 20 months were reviewed. Only patients with high-risk ulcer stigmata (arterial bleeding, oozing, nonbleeding visible vessel or adherent clot) were included. Patients receiving IV PPI before endoscopy (before group) were compared with those who received it after endoscopy (after group) with respect to endoscopic findings and, secondarily, to patient demographics and clinical outcomes.

RESULTS: The demographics and baseline characteristics of the before group (n=57) and the after group (n=109) were similar. The before group was more likely to have had IV PPI started outside of daytime hours, and median time to endoscopy in patients admitted with upper gastrointestinal bleeding was 24 h (interquartile range 9.5 to 35) in the before group and 11.3 h (interquartile range 3.7 to 17.2) in the after group (P<0.0001). At the time of endoscopy, 33% of patients in the before group had actively bleeding lesions (Forrest 1a or 1b) compared with 54% in the after group (P=0.01), but there were no significant differences in rebleeding, surgical rates, intensive care unit admission or death between the groups.

CONCLUSION: IV PPI infusions before endoscopy may lower the proportion of actively bleeding peptic ulcer lesions at endoscopy, but this finding does not appear to affect rates of rebleeding, surgery or death.

Key Words: Gastrointestinal hemorrhage; Intravenous; Pantoprazole; Retrospective

Intravenous forms of proton pump inhibitors (IV PPI) have been available for clinical use for over 10 years (1). Prospective randomized trials have shown efficacy in preventing rebleeding from high-risk peptic ulcers (defined as active bleeding or presence of a nonbleeding visible vessel) after endoscopic therapy using a bolus followed by continuous infusion of IV PPI (2-5). The optimal timing of administration of IV PPI is not known. In most studies, IV PPI was administered after endoscopic assessment with or without endoscopic therapy. It is not known if IV PPI administered before endoscopic therapy is beneficial, although a recent study (6) in abstract form suggests that this practice may reduce endoscopic signs of bleeding and the need for hemostatic therapy. A recent review of our usage patterns of IV PPI revealed that infusions

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METHODS

Patients
All patients who received IV pantoprazole (PANTO IV; Altana Pharma Inc, Canada) and upper endoscopy for the indication of bleeding from high-risk peptic ulcer stigmata (defined below) between November 1999 and June 2001 (20 months) in six hospitals in the metropolitan Vancouver area were reviewed retrospectively. The present study forms a subanalysis of a comprehensive review of IV PPI usage for all indications in 854 patients during the same time period published previously (7). Three of the hospitals were academic teaching hospitals and three were nonacademic secondary or tertiary care hospitals. The institutional review boards of each hospital gave full approval for the study.

Every instance of IV PPI usage over the study time frame was identified from hospital pharmacy databases and correlated with patient charts. All other information, including timing of administration of IV PPI, was obtained from the patient’s hospital chart. Endoscopic findings were gathered from dictated reports, endoscopic pictures and/or chart notes.

Drugs
The IV formulation of the PPI pantoprazole was approved in Canada in 1999. No other IV PPI were approved for use in Canada during the time period of the present study. All patients received a bolus dose of pantoprazole (80 mg in 95% of patients, with the remainder receiving 40 mg) followed by an 8 mg/h infusion (in 98% of patients, with higher infusion rates in the remainder). Because the goal of the present study was to analyze the effect of IV PPI in relation to endoscopic diagnosis and management of bleeding peptic ulcer, any patient who had IV PPI started more than 48 h before or after endoscopy was excluded.

Sources of information
Data were abstracted from charts by an investigator (CNA) and two research assistants using a standardized information template. Abstractors had ongoing supervision for maintenance of data quality. The template included information on timing, dose and duration of administration of IV PPI; indications for use; sociodemographic information (including age, sex, number and type of comorbid medical conditions; and risk factors for PUD including recent nonsteroidal anti-inflammatory use or a previous history of PUD); lowest pre-endoscopy hemoglobin; lowest pre-endoscopy systolic blood pressure; elapsed time between emergency department arrival and endoscopy; endoscopic findings and intervention; and outcomes including transfusion requirements, rebleeding, surgery, need for intensive care unit (ICU) admission and death.

Comorbidity was scored using the Charlson index (8), a well-validated score (9) which assigns points to 19 conditions, giving a predictive relative risk of one-year mortality from comorbid conditions. A higher score correlates with higher comorbidity. Because ulcer disease is one of the index comorbidities, the minimum score in this study was 1.

The Rockall score (10) (a validated predictor of mortality due to UGI hemorrhage) was calculated for each patient. The complete score uses data on age, presence of shock, comorbidity, cause of bleed and major stigmata of recent hemorrhage (using endoscopic findings) to predict mortality. The initial score (measured before endoscopy) uses data on age, presence of shock and comorbidity only. The range of possible scores is from 0 to 7 for the initial score and 0 to 11 for the complete score, with a higher score predictive of higher mortality.

Definitions
High-risk peptic ulcer stigmata were defined as arterial bleeding (corresponding to Forrest class 1a), active oozing (Forrest 1b), presence of a nonbleeding visible vessel (Forrest 2a) or adherent clot (Forrest 2b). Endoscopic therapy was defined as any injection therapy, heater probe, hemoclip or bipolar electrocautery undertaken at the bleeding ulcer site to control or prevent further bleeding.

Because UGI bleeding may not immediately be recognized on admission, may only be one of a list of admission diagnoses or may have been treated with IV PPI but did not have UGI hemorrhage coded, patients were considered to be admitted with UGI bleeding if IV PPI was started or endoscopy performed within 24 h of admission to hospital. The remainder of the patients had UGI bleeding while hospitalized for other reasons. Patients who had ceased to have acute medical issues but who were then waitlisted for extended care facilities on the same admission were deemed to be discharged on the date they were waitlisted for an alternate level of care.

Outcome definitions
Rebleed was defined as a postresuscitation drop in hemoglobin of 20 g/L or higher, a sudden drop in systolic blood pressure (more than 20 mmHg) unexplained by medications, or evidence of new hematemesis or melena stool. Only rebleeds that occurred during the same admission and within 30 days of initial bleed were included.

Surgery was defined as any laparotomy undertaken for control of UGI bleeding or perforation from any source after identification and/or resuscitation of the initial UGI bleed.

ICU admission was defined as admission to an ICU for monitoring or hemodynamic instability as a direct result of UGI hemorrhage. Patients who developed GI bleeding while admitted to an ICU for other reasons were not included in this measurement. Typically, in the Vancouver area, patients with routine UGI bleeding are not admitted to the ICU. Patients usually require multiorgan system failure to gain access to an ICU.

Death was defined as death from any cause during the same admission that occurred within 30 days of initial UGI bleeding. Because most deaths in the context of UGI bleeding are due to sequelae of bleeding or comorbidities as opposed to direct exsanguination, all deaths were included. Patients discharged alive in less than 30 days were not followed further.
RESULTS

Population

One hundred sixty-six patients met the study criteria, with 57 receiving IV PPI before endoscopy (before group) and 109 receiving it after endoscopy (after group). There were no significant differences between the groups with respect to age, sex, length of stay, comorbidity index, initial Rockall score (data not shown), complete Rockall score, history of previous PUD or nonsteroidal anti-inflammatory drug use, lowest hemoglobin and lowest systolic blood pressure (Table 1). A similar proportion of patients received IV PPI before endoscopy in both academic teaching hospitals and community hospitals (data not shown).

Most patients had comorbidities with a median of 2 to 3 points on the Charlson comorbidity index. This stable degree of comorbidity is due to the fact that nearly one-half of the patients did not present to hospital with UGI hemorrhage, but rather, developed the condition while hospitalized for another reason.

Timing of IV PPI administration and endoscopy

The group receiving IV PPI before endoscopy received a median of 14.3 h (interquartile range [IQR] 6.0 to 25.1, range 0 to 45) of IV PPI infusion by the time of endoscopy. In the other group, a median 3.5 h (IQR 1.9 to 6.7, range 0 to 37) elapsed after endoscopy before commencement of IV PPI therapy (Table 2).

The time from admission to endoscopy was significantly different in patients admitted with GI bleed (approximately one-half the patients in each arm), with a median of 24 h in the group receiving IV PPI before endoscopy and 11 h in those receiving IV PPI after endoscopy. The before group also had 70% of IV PPI infusions started outside of usual daytime hours (07:00 to 18:00), which was significantly higher than the after group (49%, P<0.01). Both groups had a similar proportion of endoscopies performed outside of usual daytime hours (approximately 25%). Both groups received a similar median duration of IV PPI infusion.

TABLE 2
Timing of intravenous proton pump inhibitor (IV PPI) administration and endoscopy in study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV PPI before endoscopy (n=57)</th>
<th>IV PPI after endoscopy (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of IV PPI infusion until endoscopy, median hours (IQR)</td>
<td>14.3 (6.0–25.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time elapsed after endoscopy until IV PPI infusion started, median hours (IQR)</td>
<td></td>
<td>3.5 (1.9–8.7)</td>
<td></td>
</tr>
<tr>
<td>IV PPI infusion started outside of daytime hours (07:00–18:00), n (%)</td>
<td>40 (70)</td>
<td>53 (49)</td>
<td>0.008</td>
</tr>
<tr>
<td>Endoscopy performed outside of daytime hours (07:00–18:00), n (%)</td>
<td>14 (25)</td>
<td>29 (27)</td>
<td>0.775</td>
</tr>
<tr>
<td>Time to endoscopy from admission, median hours (IQR)*</td>
<td>24 (9.5–35)</td>
<td>11.3 (3.7–17.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total duration of IV PPI infusion, median hours (IQR)</td>
<td>72 (43–107)</td>
<td>67 (39–89)</td>
<td>0.183</td>
</tr>
</tbody>
</table>

*Based on patients admitted with upper gastrointestinal bleeding only (n=29 in before group, n=59 in after group). IQR Interquartile range

DISCUSSION

At the hospitals surveyed, many patients presenting with suspected UGI bleeding received IV PPI infusions before receiving endoscopy (7). In the present study, all patients with high-risk bleeding peptic ulcers who received IV PPI were analyzed. There were no significant baseline differences between those who received IV PPI before and those who received it after endoscopy.

At the time of endoscopy, significantly fewer patients in the group receiving IV PPI before endoscopy (33%) had active ulcer bleeding (Forrest 1a or 1b lesions) than in the after group (54%) (P=0.011) (Table 3). A similar proportion of patients in both groups received endoscopic intervention (injection therapy, heater probe or bipolar electrocautery).

There were no significant differences in the rates of rebleeding, surgical intervention, need for ICU admission or death within 30 days between the two groups.

TABLE 3
Patient demographics, risk factors and baseline clinical values

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV PPI before endoscopy (n=29)</th>
<th>IV PPI after endoscopy (n=59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>64.2 (17.7)</td>
<td>66.2 (16.1)</td>
<td>0.472</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>19 (33)</td>
<td>45 (41)</td>
<td>0.318</td>
</tr>
<tr>
<td>Length of stay, median days (IQR)</td>
<td>7 (5–15.5)</td>
<td>8 (5–20)</td>
<td>0.412</td>
</tr>
<tr>
<td>Charlson comorbidity index, median points (IQR)</td>
<td>2 (2–4)</td>
<td>3 (2–4)</td>
<td>0.891</td>
</tr>
<tr>
<td>Endoscopy performed outside of daytime hours (07:00–18:00), n (%)</td>
<td>14 (25)</td>
<td>29 (27)</td>
<td>0.775</td>
</tr>
<tr>
<td>IV PPI infusion started outside of daytime hours (07:00–18:00), n (%)</td>
<td>40 (70)</td>
<td>53 (49)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hemoglobin, mean g/L (SD)</td>
<td>76 (18.4)</td>
<td>71 (17.8)</td>
<td>0.144</td>
</tr>
<tr>
<td>Systolic blood pressure, mean mmHg (SD)</td>
<td>93 (18)</td>
<td>96 (20)</td>
<td>0.362</td>
</tr>
</tbody>
</table>

IQR Interquartile range; IV PPI Intravenous proton pump inhibitor; NSAID Nonsteroidal anti-inflammatory drug; PUD Peptic ulcer disease; UGI Upper gastrointestinal

Statistical analysis

This was a retrospective study of all patients meeting inclusion criteria over the study period; a statistical power calculation was not performed. Differences between the means of continuous variables with apparently normal distributions were assessed using Student’s t test. Categorical and ordinal variables, and continuous variables with potentially skewed distributions, were compared using the Mann-Whitney U test. Differences in group proportions were analyzed with the Pearson χ² test, or the Fisher Exact Test if sample sizes were less than five. Two-tailed tests of significance at the P<0.05 level were used to determine statistical significance.
TABLE 3

Endoscopic findings and patient outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV PPI before endoscopy (n=57)</th>
<th>IV PPI after endoscopy (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pumping</td>
<td>5 (9)</td>
<td>10 (9)</td>
<td>0.047</td>
</tr>
<tr>
<td>Oozing</td>
<td>14 (25)</td>
<td>49 (45)</td>
<td></td>
</tr>
<tr>
<td>Nonbleeding visible vessel</td>
<td>24 (42)</td>
<td>27 (25)</td>
<td></td>
</tr>
<tr>
<td>Adherent clot</td>
<td>14 (25)</td>
<td>23 (21)</td>
<td></td>
</tr>
<tr>
<td>Active bleeding on endoscopy, n (%)*</td>
<td>19 (33)</td>
<td>59 (54)</td>
<td>0.011</td>
</tr>
<tr>
<td>Endoscopic therapy, n (%)</td>
<td>39 (68)</td>
<td>73 (67)</td>
<td>0.850</td>
</tr>
<tr>
<td>Transfusion needs, median units PRBC (IQR)</td>
<td>4 (2–8)</td>
<td>4 (2–7)</td>
<td>0.381</td>
</tr>
</tbody>
</table>

*Active bleeding defined as arterial pumping or oozing (Forrest 1a or 1b). IQR Interquartile range; IV PPI Intravenous proton pump inhibitor; PRBC Packed red blood cells

There are three possible explanations for this finding. First, in the majority of patients, the natural course of bleeding peptic ulcer is to spontaneously cease bleeding (11-13). The median time to endoscopy from admission was significantly longer in the group receiving IV PPI before endoscopy (24 h) than in the after group (11 h). Therefore, it is possible that the longer time to endoscopy would account for less actively bleeding lesions. For example, it could be hypothesized that those patients who could wait for endoscopy until a more convenient time simply had IV PPI infusions started in the interim. This idea is supported by the finding that the majority of patients who had IV PPI before endoscopy had it started outside of daytime hours. However, both groups had a similar prima facie assessment of the severity of GI bleeding based on the similar burden of comorbidity, hemodynamic status and initial Rockall scores at the time of presentation with bleeding. Although other unmeasured factors may have contributed to the timing of endoscopy, it appears the severity of bleed and comorbidity (at least in the variables measured in this analysis) did not appear to play a role in the decision-making process of when to start IV PPI infusions.

Alternatively, it is possible that IV PPI infusions may decrease the amount of active bleeding (‘downstaging’ the lesions) over time compared with no medical therapy at all, with the biological rationale that increasing intragastric pH allows improved blood clot formation and more rapid slowing of blood loss compared with volume resuscitation alone. This effect was seen in a prospective trial of oral PPI for bleeding peptic ulcer where a reduction in rebleeding was seen in the absence of endoscopic hemostatic therapy (14). This finding was also seen in a large double-blind randomized control study of 1147 UGI bleed patients randomly assigned to intermittent IV omeprazole boluses or placebo before endoscopy, where significantly fewer patients in the omeprazole group had endoscopic signs of UGI bleeding (33%) compared with the placebo group (45%) (15). More recently, a prospective randomized trial of IV omeprazole or placebo before endoscopy showed similar findings, with less hemostatic therapy required in the omeprazole group; however, this study has only been presented in abstract form (6).

A third contributing factor is the interobserver variability in endoscopic recognition of high-risk stigmata of bleeding. Although studies have shown wide interobserver variability for definition of high-risk stigmata (16), correlation is higher within institutions (13,17) and interobserver agreement is good for active bleeding (17,18).

Whichever explanation is correct is unclear. However, the present study suggests that it may be a safe practice to start IV PPI early and, if necessary, to delay endoscopy to address other medical issues. Thus, the use of early IV PPI may ‘downstage’ lesions without detracting from clinical outcomes. The clinician must keep in mind, however, that endoscopic assessment and hemostatic therapy is the definitive treatment and standard of care for bleeding peptic ulcer; IV PPI is not a substitute for this therapy.

In terms of the cost of this practice, a study by Enns et al (19) compared a strategy of empirically treating all patients presenting to the emergency department with IV PPI infusion and endoscopic treatment versus endoscopic treatment alone using a statistical model of a hypothetical cohort of 1000 patients. Based on the expected frequencies of endoscopically treatable ulcers and efficacy of IV PPI from the landmark IV PPI study by Lau et al (4), and using Canadian cost figures, results showed that sufficient rebleeds would be prevented to provide a net cost savings. The main caveat of this study requires stopping IV PPI infusions in patients who do not have high-risk ulcer stigmata on endoscopy. In our experience, this has not been the case, with the majority of patients with low-risk lesions having their infusions continued (7).

Individual physician practices and awareness, although not assessed in this study, could have also played a role in the decision process for starting IV PPI. The time period of this study began with the introduction of IV PPI into Canada, and before the landmark study by Lau et al (4), which clearly showed the benefit of IV PPI given as bolus followed by infusion after endoscopic therapy. Starting IV PPI before endoscopy was thus a reasonable practice, even though it was not evidence-based.

The high rebleeding rate may be a reflection of inadequate endoscopic treatment, which was only performed in approximately two-thirds of the patients in each group. Endoscopic hemostasis of active ulcer bleeding or visible vessels has been shown to significantly decrease rebleeding, surgery and mortality rates in two meta-analyses (20,21). Although most of the patients who did not receive endoscopic therapy in the present study had adherent clots (data not shown), recent research has suggested that aggressive treatment of clots reduces rebleed rates as well (22,23).

Mortality in the present study was high, with a rate of 11% in the group receiving IV PPI before endoscopy and 15% in the after group. This is higher than the average case-fatality rates reported in other studies, which generally range from 4% to 10% (12,24-27). However, the median complete Rockall scores of the groups of 5 and 6 (out of a possible 11), correlated with a mortality of 10.8% and 17.3%, respectively, in the original Rockall paper, with mortality for patients with rebleeding even higher than this (10). The mean lowest recorded hemoglobin (76 g/L in the before group and 71 g/L in the after group) and mean lowest systolic blood pressure in the mid-90s range suggested relatively severe peptic ulcer bleeding in the present study population. Factors that also affected the case-fatality rate were the significant comorbid illness of this group, as well as the older age of the patients.
(average over 60 years); both have been shown to increase the mortality rate (28,29).

Starting IV PPI infusions in advance of endoscopic therapy did not affect the outcome measures of rebleeding, transfusion requirements, need for surgery or ICU admission or death. Although there was significantly lower active bleeding seen at the time of endoscopy in the group given IV PPI beforehand, the significance of this finding is not clear. The fact that the outcomes were similar in the group receiving IV PPI before endoscopy, even though the time to endoscopy was longer for these patients, suggests that IV PPI infusions may allow the clinician to delay endoscopy (to focus on more pressing patient comorbidities, for example, or until regular opening hours of the clinician’s endoscopy suite) without jeopardizing the patient’s ultimate outcome. The hypothesis that early administration of IV PPI ‘downstages’ lesions is supported by the present study; however, due to the retrospective nature of this database, inherent flaws are present that limit the strength of this inference.

Results of prospective studies in the arena of early IV PPI administration are awaited and will no doubt raise further questions, such as the optimal duration of prior IV PPI and its relationship to timing of endoscopy.

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10. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment comes were similar in the group receiving IV PPI before endoscopy, even though the time to endoscopy was longer for these patients, suggests that IV PPI infusions may allow the clinician to delay endoscopy (to focus on more pressing patient comorbidities, for example, or until regular opening hours of the clinician’s endoscopy suite) without jeopardizing the patient’s ultimate outcome. The hypothesis that early administration of IV PPI ‘downstages’ lesions is supported by the present study; however, due to the retrospective nature of this database, inherent flaws are present that limit the strength of this inference. Results of prospective studies in the arena of early IV PPI administration are awaited and will no doubt raise further questions, such as the optimal duration of prior IV PPI and its relationship to timing of endoscopy.
