Research Report

Intermittent Versus Continuous Infusion Dosing of Intravenous Proton Pump Inhibitors for Upper Gastrointestinal Bleeding

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Abstract

BACKGROUND: Proton pump inhibitor (PPI) continuous infusions or intermittent boluses are used for the treatment of upper gastrointestinal bleeding (UGIB). Intermittent boluses are easier to give and are of lower cost without affecting clinical outcomes. **OBJECTIVE:** To compare the rate of rebleeding between intermittent bolus and continuous infusion PPI therapy. **METHODS:** We performed a retrospective, multicenter review of patients with UGIB receiving either continuous or intermittent PPI therapy. During the study period, due to drug and supply shortages, each institution implemented policies preferring intermittent PPI bolus therapy. We performed bivariate and multivariable comparisons of the 2 treatment strategies, with the primary outcome of interest being incidence of rebleeding. Additional variables of interest included intensive care unit (ICU) and hospital lengths of stay, discharge disposition, and in-hospital mortality. **RESULTS:** Compared with intermittent bolus dosing (n = 209), patients receiving continuous infusion PPI (n = 237) were associated with a higher rate of rebleeding (33.8% vs 23.0%; $P = 0.012$); however, no difference was detected in multivariable analysis: adjusted odds ratio, 1.50 (95% confidence interval, 0.91-2.50). There was no difference in median hospital or ICU length of stay, discharge disposition, or in-hospital mortality. Correlatively, patients receiving continuous infusion therapy were more likely to have liver disease (29.1% vs 20.1%; $P = 0.028$), alcohol use disorder (28.3% vs 16.3.%; $P = 0.003$), history of lower gastrointestinal bleeding (6.4% vs 1.9%; $P = 0.021$), variceal bleeding (6.3 vs 2.4%, $P = 0.045$), and be admitted to the ICU (65.0% vs 32.5%, $P = 0.00$). **CONCLUSIONS:** Introduction of intermittent PPI bolus UGIB treatment via change in hospital policy was not associated with higher rates of rebleeding. However, continuous PPI therapy may have been perceived as more effective as it was used more commonly in high-risk patients.

Keywords

upper gastrointestinal bleeding, proton pump inhibitors, continuous infusion

Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical condition that can lead to life-threatening emergencies requiring prompt medical intervention. In the United States, UGIB annually accounts for more than 300 000 hospitalizations with an estimated cost of $2.5 billion.[1,2] Generally, UGIB is associated with nonsteroidal antiinflammatory drug use and *Helicobacter pylori* infection.[3] The mortality rate due to all forms of UGIB is approximately 10%.[4]

To manage ulcerative bleeding, the current 2021 American College of Gastroenterology (ACG) guidelines recommend hemodynamic resuscitation, endoscopic hemostasis, and administration of proton pump inhibitors (PPIs).[5-7] PPIs maintain high intragastric pH, allowing for clot formation, inhibition of clot degradation, and decreasing the risk of rebleeding. Because of the relatively short half-life of PPIs, guidelines during the study period recommended the use of continuous intravenous (IV) PPI after

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endoscopy to maintain a constant pH above 6.[2,6,8] However, various studies have demonstrated that intermittent dosing of IV PPIs compared with placebo or no therapy is as efficacious as continuous PPI dosing.[9] The most recent ACG guidelines now recommend either continuous infusion or intermittent bolus PPI therapy.[7]

In 2013, a Cochrane review of 22 randomized controlled trials evaluating continuous infusion versus intermittent dosing of PPIs found no significant differences in mortality, rebleeding, hospital length of stay, or need for urgent interventions.[10] A double-blind randomized comparative study conducted by Uçbilek et al in 2014 demonstrated that patients with peptic ulcer bleeding treated with either high-dose infusion or low-dose bolus of pantoprazole had similar efficacy outcomes after endoscopy.[11] In a 2014 systematic review and meta-analysis conducted by Sachar et al, the risk of rebleeding within 7 days with intermittent PPI therapy was noninferior to that of continuous infusions.[12] These studies all suggest that the usage of intermittent administration offers benefits such as lower cost and ease of administration. However, in 2020, a smaller single-center retrospective cohort study conducted by Khan et al found that patients treated with bolus intravenous PPI therapy were associated with worse outcomes, including the increased need for additional interventions.[13] While the most recent guidelines do recommend intermittent PPI therapy, there is no consensus regarding the PPI agent, dose, or frequency. The objective of this study was to compare intermittent and continuous infusion PPI therapy in the empiric treatment of UGIB at 2 large academic medical centers.

Materials and Methods

Study Design and Setting

This multicenter retrospective cohort study was conducted in adult patients who were admitted to 2 hospitals between March 1, 2016, and August 31, 2019. Hospital 1 is a 600-bed academic teaching hospital located in California, and Hospital 2 is a 576-bed academic teaching hospital located in Oregon. Driven by drug and supply shortages, both hospitals implemented continuous PPI sparing strategies. In June 2018, a best practice advisory was implemented at Hospital 1 recommending providers to use intermittent PPI boluses over continuous infusions for UGIB. Providers were allowed to order continuous infusion PPI, but were prompted in the order menu to acknowledge that they understood the institutional preference and provide documentation of the clinical rationale for PPI infusion therapy. Similarly in November 2017, at Hospital 2, continuous infusion dosing was restricted. However, Hospital 2 protocol required a pharmacy request and approval for all continuous PPI infusions (ie, providers were not able to directly order continuous infusion therapy).

Study Participants and Intervention

Patients met inclusion criteria if they were 18 years of age or older and were admitted via the emergency department (ED) or into an intensive care unit (ICU). Patients who underwent gastrointestinal endoscopy at the admitting hospital and who received parenteral PPIs for empiric therapy of UGIB were assessed for outcomes. The frequency of intermittent dosing was restricted to esomeprazole or pantoprazole 40 mg twice daily. Those with once-daily regimens were excluded due to uncertainty of adequate acid suppression required to reduce rebleeding. Patients were additionally excluded if they were pregnant, incarcerated, did not receive an endoscopy, or had an outside hospital endoscopy performed. The study underwent expedited review and was approved by both hospitals' Institutional Review Boards. Given the retrospective nature of this study, the requirement for informed consent was waived.

Data Collection

All patient data were extracted from the electronic medical record. Patients at both study sites who received IV PPIs in the ED or ICU were identified through administration records for an UGIB encounter diagnosis. Data were collected using a standardized query form in the Research Electronic Data Capture (REDCap) data management system that was created and piloted before official data collection began.[14] During data collection, the data were audited periodically for accuracy and nonsensical values.

Primary Measure of Interest

The primary measure of interest was the incidence of rebleeding 48 hours after endoscopy, defined as receiving $\geq$1 unit of blood product or requiring additional endoscopic, radiological, or surgical interventions. Secondary outcomes included hospital and ICU length of stay, discharge disposition, and in-hospital mortality.

Statistical Analysis

For bivariate analysis, based on the currently published literature, the projected sample size to detect a 15% difference in the primary outcome was 324 patients between well-balanced groups.[11] Continuous variables such as age were compared using the Student *t* test or the Wilcoxon signed-rank sum test, as appropriate. Dichotomous data were compared using the χ^2 or Fisher exact test. Statistical significance was defined by a 2-sided *P* value of 0.05. Data are described using proportions, means or medians, and interquartile ranges.

For multivariable analysis, a logistic regression was performed evaluating the effect of PPI dosing strategy on rate of rebleeding controlling for age, sex, weight, initial heart rate

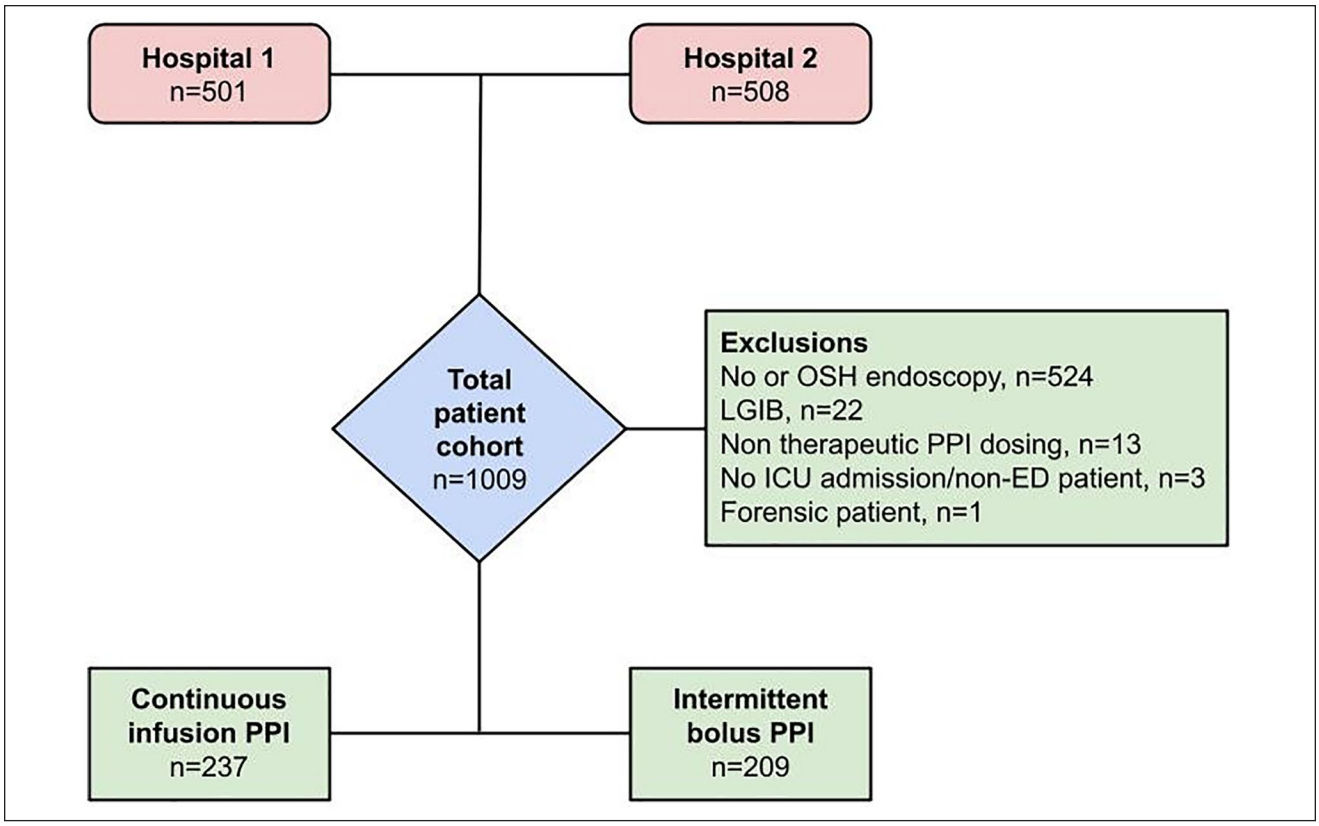

Figure 1. Cohort assembly.
Abbreviations: ED, emergency department; ICU, intensive care unit; LGIB, lower gastrointestinal bleed; OSH, outside hospital; PPI, proton pump inhibitor.

and mean arterial blood pressure, ICU admission, length of stay, disposition, medical history, and comorbidities (ie, renal or liver disease, alcohol use disorder, or disseminated malignancy), prior to admission medications increasing risk for bleeding or gastrointestinal complications (ie, anticoagulation, antiplatelet, histamine-2 receptor blockers [H2RAs], PPIs, and systemic corticosteroids), and initial renal and liver function. The logistic model specification was confirmed via link test, performance via Hosmer-Lemeshow goodness of fit test, and discrimination via receiver operating characteristics. Patients with the highest influence/leverage were analyzed by comparing predicted values, residuals, leverage statistics, and coefficient of influence. Influential patients were not excluded if there was no significant effect on coefficients. Predictor overlap was evaluated with propensity scores and identified a lack of overlap largely due to differences in admission to ICU and length of hospital stay; however, both predictors were included in the analysis.

Results

A total of 501 records from Hospital 1 and 508 records from Hospital 2 were identified and reviewed between March 1, 2016, and August 31, 2019. After exclusion, a total of 237 patients receiving continuous infusion and 209 intermittent bolus were included in the bivariate analysis. For multivariable analysis, we excluded patients with missing initial laboratory values, resulting in 408 unique encounters available for modeling. The full cohort assembly and exclusion criteria are shown in Figure 1.

There were no significant differences in age, sex, body mass index, prior to admission medications that may predispose bleeding (anticoagulants, antiplatelets, steroids), or use of acid suppression therapy (PPIs and H2RAs). Patients in the continuous infusion PPI therapy group had a greater prevalence of liver disease (29.1% vs 20.1%; $P = 0.028$), alcohol use disorder (28.3% vs 16.3%; $P = 0.003$), history of lower gastrointestinal bleeding (6.4% vs 1.9%; $P = 0.021$), and variceal bleeding (6.3 vs 2.4%; $P = 0.045$). In addition, patients in the continuous infusion group had slightly, but significantly worse liver function tests and higher heart rates at presentation (Table 1).

Primary Measure of Interest—Rebleeding

Bivariate analysis. Patients who received continuous infusion PPI therapy had a greater incidence of rebleeding (33.8% vs 23.0%; $P = 0.012$). These patients also required

Table 1. Population Demographics.

Characteristics	Continuous N = 237	BID N = 209	*P* value
Age, mean (SD)	62.2 (15.3)	64.1 (17.6)	0.22
Male, n (%)	158 (66.7)	130 (62.2)	0.33
BMI, mean (SD)	26.8 (6.9)	26.2 (6.5)	0.31
Medical history PTA, n (%)			
Renal disease	31 (13.1)	27 (12.9)	0.96
Liver disease	69 (29.1)	42 (20.1)	0.028
Alcohol use disorder	67 (28.3)	34 (16.3)	0.003
Disseminated malignancy	18 (7.6)	14 (6.7)	0.71
Gastrointestinal bleeding history PTA, n (%)			
Upper GI	67 (28.3)	55 (26.3)	0.64
Lower GI/Diverticular	15 (6.3)	4 (1.9)	0.021
Variceal	15 (6.3)	5 (2.4)	0.045
None	149 (62.9)	146 (69.9)	0.12
PTA medications, n (%)			
Anticoagulant	43 (18.1)	38 (18.3)	0.97
Antiplatelet	88 (37.1)	89 (42.6)	0.24
Acid Suppression	83 (35.0)	87 (41.6)	0.15
Steroids	13 (5.5)	16 (7.7)	0.35
Labs and vital signs on presentation			
Hemoglobin, mean (SD)	8.4 (2.6)	8.9 (2.5)	0.054
Hematocrit, mean (SD)	25.7 (7.3)	27.1 (7.3)	0.054
BUN, median (IQR)	30 (19-46)	28 (18-41)	0.20
Creatinine, median (IQR)	0.9 (0.7-1.3)	0.9 (0.7-1.4)	0.79
AST, median (IQR)	29 (21-57)	25 (19-38)	0.013
ALT, median (IQR)	24 (17-40)	20 (15-32)	0.022
AlkPhos, median (IQR)	68 (49-115)	69 (50-95)	0.48
TBili, median (IQR)	0.7 (0.5-1.2)	0.6 (0.4-1.0)	0.035
MAP, mean (SD)	80.7 (17.3)	81.9 (15.1)	0.44
HR, mean (SD)	91.0 (20.5)	85.6 (16.2)	0.002

Abbreviations: ALT, alanine transaminase; AlkPhos, alkaline phosphatase; AST, aspartate aminotransferase; BID, twice daily; BUN, blood urea nitrogen; GI, gastrointestinal; HR, heart rate; IQR, interquartile range; MAP, mean arterial pressure; PTA, prior to admission; SD, standard deviation; TBili, total bilirubin.

additional blood product administration after endoscopy (33.3% vs 22.5%; $P = 0.011$). No statistically significant differences were identified in the need for surgical interventions (Table 2).

Multivariable analysis. Compared with intermittent dosing of PPIs and holding all other predictors constant, continuous infusion dosing had no significant difference in rates of rebleeding with an adjusted odds ratio (OR) of 1.50 (95% confidence interval [CI], 0.91-2.50). No other variables were found to be significant predictors of rebleeding. The overall model R^2 was 0.11 and $P = 0.008$ (Supplemental Appendix 1).

Other measures of interest. Patients receiving continuous infusion therapy were more likely to be admitted to the ICU (65.0% vs 32.5%; $P = 0.00$). There were no differences in hospital or ICU length of stay, discharge disposition, or in-hospital mortality (Table 3).

Discussion

Recent drug and supply shortages have resulted in hospitals implementing mitigation strategies. We report on 2 hospitals that changed their protocols to provide evidence-based therapy for treatment of UGIB while conserving medications and resources. Our data show that the implementation of preferential intermittent PPI bolus strategy for UGIB treatment was not associated with worse outcomes compared with usual care with continuous PPI infusion therapy; however, our data also reveal an interesting practice pattern.

In multivariable analysis, when all other predictors were controlled, there was no difference in rebleeding complications between continuous infusion and intermittent bolus PPI groups following endoscopy intervention. However, bivariate analysis revealed a few points worth highlighting. First, there were significant differences in baseline characteristics. Patients receiving continuous infusion PPI were

Table 2. Primary Outcomes: Incidence of Rebleeding Rates (48 Hours After Endoscopy).

Endpoints	Continuous N = 237	BID N = 209	*P* value
Rebleeding, n (%)	80 (33.8)	48 (23.0)	0.012
Blood product administration, n (%)	79 (33.3)	47 (22.5)	0.011
pRBCs, mean (SD)	2.7 (2.1)	2.1 (1.4)	0.10
Plts, mean (SD)	1.5 (0.6)	1.5 (0.5)	1.00
FFP, mean (SD)	2.6 (1.6)	2.6 (3.0)	0.97
Cryo, mean (SD)	1.0 (-)	1.5 (0.7)	0.67
Surgical intervention, n (%)	10 (4.2)	5 (2.4)	0.29
Repeat endoscopy, n (%)	9 (3.8)	4 (1.9)	0.24
Surgery, n (%)	1 (0.4)	1 (0.5)	0.93

Abbreviations: BID, twice daily; Cryo, cryoprecipitate; FFP, fresh frozen plasma; pRBCs, packed red blood cells; Plts = platelets; SD, standard deviation.

Table 3. Secondary Outcomes.

Endpoints	Continuous N = 237	BID N = 209	*P* value
Hospital LOS in hours, median (IQR)	92 (68-128)	82 (52-138)	0.10
ICU admission, n(%)	154 (65.0)	68 (32.5)	0.00
ICU LOS in hours, median (IQR)	41 (25-66)	40 (22-96)	0.31
Discharge disposition home, n (%)	196 (85.6)	174 (87.4)	0.85
Discharge disposition SNF/Rehab, n (%)	30 (13.1)	23 (11.6)	
Discharge disposition Other, n (%)	3 (1.3)	2 (1.0)	
In-hospital mortality, n (%)	7 (3.0)	9 (4.3)	0.44

Abbreviations: BID, twice daily; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SNF, skilled nursing facility.

high-risk patients, with more frequent history of liver disease, alcohol use disorders, and previous gastrointestinal bleeding. Second, patients in the continuous PPI group had a higher severity of illness at baseline. The admission hemoglobin and hematocrit were lower, liver function tests higher (including total bilirubin), and patients had an increased heart rate. Finally, continuous infusion therapy was associated with an increased rate of ICU admission. Providers were more likely to order continuous infusion PPI therapy for these patients, regardless of the electronic health record prompts and barriers. While the outcomes of this study can be attributed to a systematic change, provider preference still had an important influence on dosing strategy. It may be possible that continuous infusion may be perceived as a stronger and more effective therapy and was chosen for high-risk patients. With the most recent ACG guideline update equating the 2 dosing strategies, hospital departments of pharmacy and stakeholders should consider this important provider bias when deciding on PPI drug selection architecture during computerized order entry.[7,15]

Intermittent therapy offers many advantages to both institutions and patients. There are indirect cost savings such as decreased use of admixing PPI infusions in an IV compounding room compared with using a directly administered bolus dose at the patient's bedside.[12] From a drug utilization perspective, a 72-hour treatment with continuous pantoprazole uses seventeen 40-mg vials, while the intermittent bolus regimen only uses 8 vials in the same time period. The cost of personnel associated with preparing and mixing the infusions also needs to be noted as continuous infusions are more labor-intensive. When considering critical care units, transitioning from a continuous to intermittent dosing regimen can result in fewer intravenous infusions, which may increase intravenous access availability and decrease overall fluid administration. There may also be other benefits that we did not assess in this study, such as patient and nursing satisfaction that would likely favor intermittent dosing over continuous regimens. At least 1 disadvantage with intermittent bolus dosing must be noted: the bedside nurse will have an additional task of reconstitution of PPI vials prior to administration. Nevertheless, such a task is relatively quick and simpler compared with IV bag mixing, line priming, and drug infusion pump programming and monitoring. Considering the most recent ACG guideline update and other operational and financial benefits of intermittent PPI strategy, we anticipate an overall decrease in the use of PPI infusions for UGIB treatment.[7,15]

Limitations

We are limited by the retrospective nature of our study and inherent bias of such study design. However, care was taken to accurately extract and confirm collected data. As we are restricted to only the data that were documented, we are unable to comment on PPI therapy beyond pantoprazole and esomeprazole. In addition, only comparisons between continuous and twice-daily intermittent dosing were assessed. The patient populations from 2 different hospitals are represented in our data and our results may not be generalizable. In addition, each hospital may have had different treatment protocols and practice patterns which we did not measure that may have affected the outcome. Many patients in our study did not have an identified source of bleeding or documented Forrest Classification, and our outcomes may not be representative of patients with confirmed sources of bleeding. While the multivariable analysis limits certain biases, we are limited by predictors and confounders that we were able to collect from patient charts. Finally, cost analysis of each therapy was not assessed and cannot be commented on.

Conclusions

A 2-hospital policy change favoring intermittent over continuous PPI therapy for UGIB was not associated with increased risk of rebleeding. However, continuous PPI therapy was more commonly associated with higher risk patients.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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