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Comparative Analysis of Continuous versus Intermittent Proton Pump Inhibitor Therapy in Patients with Upper Gastrointestinal Bleeding Due to Ulcers

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Abstract

Upper gastrointestinal bleeding (UGIB) presents as a prevalent clinical challenge, with annual incidence rates ranging from 80 to 150 cases per 100,000 individuals. Guidelines for managing patients with UGIB due to bleeding ulcers recommend a continuous infusion of proton pump inhibitors (PPI). However, studies comparing intermittent dosing of PPI therapy show that this regimen achieves similar clinical benefits. If the clinical efficacy remains equivalent, intermittent dosing will be more cost-effective for patients and the health care system. Our research study **aims to analyze** the comparative effectiveness of intermittent versus continuous PPI therapy after endoscopic treatment in patients with UGIB, focusing on such endpoints as rebleeding risk at 3- and 7-day mortality rates. **Methods:** Resources searched included MEDLINE, EMBASE, PUBMED, and the Cochrane Central Register of Controlled Trials databases from January 2010 through December 2023 with the inclusion of meta-analysis, systematic review, review, or ACG guideline recommendations. **Results** of the analysis show how recommendations regarding high vs. low PPI regimen changed over time: from no difference in regimen in 2010 to recommending continuous regimen in 2012 to declaring insufficient evidence between choosing one regimen over another in 2013 to determine that both regimens were comparable to each other in 2014-2018 and finally to recommending both regimens in 2021. To **conclude**, our review shows that in patients with bleeding ulcers and high-risk endoscopic findings, intermittent PPI therapy is non-inferior to continuous PPI infusion for three days, seven days bleeding risk or mortality rates; however, it remains challenging to determine the most optimal intermittent regimen due to heterogeneity of RCTs included in meta-analyses, and further trials will need to

be performed.

Keywords

Upper Gastrointestinal Bleeding, PPI, Continuous, Intermittent, Bolus, Regimens, Review

1. Introduction

Upper gastrointestinal bleeding (UGIB) presents as a prevalent clinical challenge, with annual incidence rates ranging from 80 to 150 cases per 100,000 individuals, associated with 2% and 15% mortality rates in the United States [1]. Ulcers remain the number one cause of upper gastrointestinal bleeding in the United States [2]. The economic impact is substantial, with hospitalization costs estimated at $ 2.5 billion in the United States, as highlighted in Kim J.'s analysis on managing and preventing UGIB [3].

Guidelines for managing patients with UGIB due to bleeding ulcers recommend a continuous infusion of proton pump inhibitor (PPI) of 80 mg, followed by an infusion of 8 mg/hour. Along with performing an endoscopy, these recommendations remain the cornerstone of treatment.

However, studies comparing intermittent dosing of PPI therapy as a bolus at timed intervals show that this regimen achieves similar clinical benefits to bolus plus continuous infusion of PPI therapy. While both regimens are seen in practice, intermittent dosing will be more cost-effective for patients and the healthcare system if the clinical efficacy remains equivalent [4] [5].

PPIs target the terminal phase of gastric acid production. The mechanism involves PPIs, being lipophilic weak bases, crossing into the acidic parietal cell canaliculus, where they irreversibly bind to the H+/K+ ATPase enzyme, effectively halting acid secretion. Due to the short half-life of PPIs of about an hour, the recommendation was made for continuous infusion in patients with UGIB. However, even though the half-life of a proton pump inhibitor is only one hour, it leads to the inhibition of approximately 70% of the acid-producing enzymes, with the impact persisting for up to 48 hours due to the irreversible nature of the enzyme binding. Moreover, according to the data from *in-vitro* studies, even an intermittent dosing schedule of PPIs can achieve up to 80% inhibition of maximum acid production, with a prolonged effect of up to 48 hours [4] [6] [7] [8] [9] [10].

In a continuous administration protocol, the total dose of proton pump inhibitor (PPI) is 656 mg, whereas, in an intermittent regimen, the total dose is twice less, only 320 mg. If intermittent PPI therapy is similarly effective as a continuous regimen, the substitution by intermittent regimen will allow for a significant decrease in cost and resource use in hospitals worldwide.

Our research study aims to perform an analysis by reviewing the comparative effectiveness of intermittent versus continuous PPI therapy after endoscopic

treatment in patients with UGIB caused by ulcers with high-risk stigmata, with a focus on such endpoints as rebleeding risk at 3- and seven days and mortality rates.

2. Research Methods

Resources searched included MEDLINE, EMBASE, PUBMED, and the Cochrane Central Register of Controlled Trials databases from January 2010 through December 2023. The following keywords were applied: continuous vs. intermittent PPI, continuous vs. bolus PPI, and high vs. low dose PPI. Inclusion criteria: a meta-analysis, systematic review, review, or ACG guideline recommendations. Exclusion criteria: clinical trials, randomized controlled trials (RCT), case reports, and book chapters (Figure 1).

The studies were reviewed independently by both authors and, after discussion, were then determined to be eligible if criteria were met.

The study inclusion and exclusion criteria and primary outcomes are outlined in the chart below.

3. Results

Here, we reviewed data from meta-analyses and ACG guidelines comparing continuous versus intermittent administration of PPIs in patients with UGIB after endoscopic treatment to 3- and 7-day rebleeding risk and mortality rate. Our analysis is presented in chronological order in Table 1 and below.

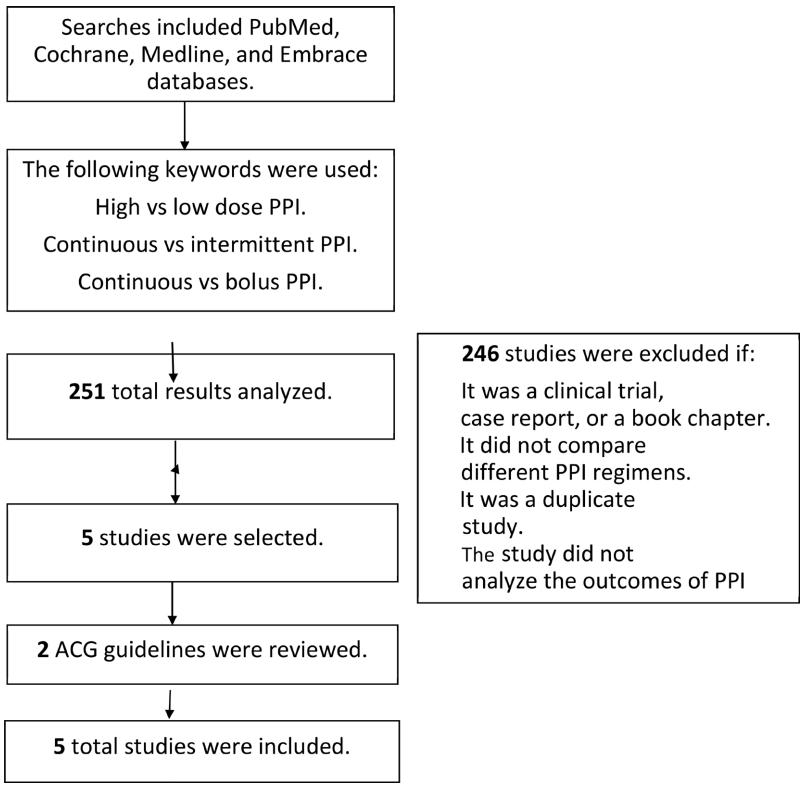

Figure 1. Summary of research method analysis.

Table 1. Summary of outcome analysis comparing continuous versus intermittent administration of PPIs in patients with UGIB after endoscopic treatment to 3- and 7-day rebleeding risk and mortality rate.

Year	Source	N of included studies/patients	Regimen	3-day rebleeding risk	7-day rebleeding risk	Mortality
2010	Wang CH *et al.* High-dose vs. non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials [11].	7 RCT including 1157 patients	80-mg bolus, followed by 8-mg/h continuous infusion for 72 hours. Continuous infusion doses exceeding 192 mg/d were also considered high-dose PPIs. Other doses were considered non-high-dose PPIs.	High-dose PPIs and non-high-dose PPIs did not differ in their effects on the rates of rebleeding OR, 1.30; 95% CI, 0.88 - 1.91.		No difference in mortality, OR 0.89; 95% CI 0.37 - 2.13.
2010	Wu LC *et al.* High-dose vs. low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis. World J Gastroenterol [12].	9 RCTs, including 1342 patients, were included in the analysis.	The dosage of PPI was considered a high dose if at least twice the low dose of any PPIs was used during the 72 hours following endoscopic hemostasis.	A high-dose PPI regimen is not superior to a low-dose PPI regimen.		A high-dose PPI regimen is not superior to a low-dose PPI regimen.
2013	Neumann I *et al.* Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. Cochrane Database Syst Rev [14].	13 RCTs (1716 patients)	"High" dose regimens are considered 72-hour cumulative doses > 600 mg of intravenous PPI compared to other doses.	Insufficient evidence for concluding results		insufficient evidence for concluding results
2014	Sachar H *et al.* Intermittent vs. continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis [15].	13 studies included in meta-analysis	80-mg intravenous bolus followed by a continuous 8-mg/h intravenous infusion for 72 hours vs boluses (they could be once daily or more often; oral vs intravenous).	Intermittent PPI regimen is comparable to bolus plus continuous infusions RR < 1	RR for intermittent vs. bolus plus continuous infusion of PPIs was 0.72	RR for mortality < 1
2018	Sgourakis G *et al.* A meta-analysis and meta-regression analysis. Turk J Gastroenterol [16].	10 RCTs included 1.651 patients.	A high-dose PPI regimen is identified as an 80 mg bolus followed by intravenous administration of 8 mg/h for 72 h; a low-dose regimen is not specified.	Significantly fewer cases of rebleeding in the low-dose PPI treatment arm		comparable outcomes.

Abbreviations: PPI-Proton Pump Inhibitors, RCT-Randomized Controlled Trials.

Results of two meta-analyses published in 2010 performed by Wang *et al.* [11] and Wu *et al.* [12] showed no significant differences in rebleeding rates or mortality between continuous and intermittent PPI regimens.

In the meta-analysis performed Wang CH *et al.* [11], 7 RCTs were included. At the same time, high-dose PPI was defined as a dose equivalent to an 80 mg bolus of omeprazole or pantoprazole, followed by continuous intravenous effusion at 8 mg/hour for 72 hours. Continuous infusion doses exceeding 192 mg/d were also considered high-dose PPIs. Other doses were considered non-high-dose PPIs; Low-dose PPIs were defined as 40 mg/d or less of intravenous or oral omeprazole or pantoprazole, and Intermediate-dose PPIs were defined as those between high and low doses of intravenous or oral omeprazole or pantoprazole. According to the results of the quantitative analysis, the odds ratio (95% confidence intervals) for rebleeding and mortality were 1.30 (0.88 - 1.91) and 0.89 (0.37 - 2.13), respectively. To summarize, no significant difference between high-dose and non-high-dose groups was noted in rebleeding or mortality. However, the severity of bleeding, as well as the ethnicity of the selected population (Asians vs Europeans) in RCTs, varied.

In a meta-analysis performed by Wu LC *et al.* [12], 9 RCTs were included; the dosage of PPI was considered high if it was at least twice the low dose of any PPIs used during the 72-h after performing endoscopic hemostasis. The results showed that high-dose intravenous PPI was not superior to low-dose intravenous PPI in reducing rebleeding [odds ratio (OR) = 1.091, 95% confidential interval (CI): (0.777 - 1.532), and mortality (OR = 1.022, 95% CI: 0.476 - 2.196). However, the type of endoscopic intervention and the type of PPI varied across studies, as well as only 4 studies were at low risk of bias.

However, two years later, in 2012, The American College of Gastroenterology (ACG) published guidelines recommending an IV PPI therapy comprising an 80 mg bolus followed by a continuous 8 mg/h infusion for 72 hours for ulcers exhibiting high-risk stigmata such as active bleeding, a non-bleeding visible vessel, or an adherent clot [13].

Cochrane's systematic review by Neumann I *et al.*, published in June 2013, concluded that the evidence was insufficient to determine the superiority, inferiority, or equivalence of high-dose PPI treatment compared to lower doses in peptic ulcer bleeding [14]. 22 RCTs were included; the risk of bias was high in 17 and unclear in 5. The primary analysis included 13 studies (1716 patients) comparing "high" dose regimens (72-hour cumulative dose > 600 mg of intravenous PPI) to other doses; however, the results of the meta-analysis concluded that there was no significant heterogeneity for any clinical outcome.

A 2014 JAMA Internal Medicine meta-analysis and systematic review by Sachar H *et al.* [15] divided selected 13 RCTs into two categories: the 1st group-control group included patients who had 80 mg intravenous bolus for a continuous 8 mg/hr. for 72 hours; in comparison, the intervention group was defined as PPI administered in intermitted doses with no restrictions in the frequency of boluses, the doses of boluses or the route of administration that could be either oral or intravenous. Results indicated the noninferiority of intermittent IV PPI BID to continuous regimens in assessing the risk of rebleeding at 3 and 7 days and mortality rates. The study noted that risk ratios for rebleeding within 3 days and

mortality were less than 1. The mean differences for blood transfusion and hospital length of stay were less than 0, signifying no increased risk with intermittent therapy [15]. However, studies included in the systematic review were of variable quality, and the risk of bias cannot be excluded.

The meta-analysis by Sgourakis *et al.* in 2018 [16] included 1651 participants from 10 randomized control trials, determining high-dose PPI as twice the low dose of any PPIs administered during the 72-hour post-endoscopic treatment with hemostasis. There were no differences in rebleeding rates, and the mortality rates were comparable. However, enrolled patients had different severity of bleeding peptic ulcer, and 2 trials analyzed the Asian population. At the same time, PPI is noted to have improved efficacy in the Asian population due to the activity of the cytochrome P450 enzyme. Interesting to see that even though the regimen of PPI did affect gastric acidity, there were no significant differences in recurrent hemorrhage rates between the two treatment groups.

Notably, the 2021 ACG guidelines expanded their recommendations, suggesting that high-dose therapy could be administered continuously, intermittently, or orally. The guidelines specify an 80-mg bolus followed by 8 mg/hr. Infusion for continuous therapy, while optimal dosing for intermittent oral or IV therapy remains less defined, though it is suggested to be an 80-mg bolus followed by 40 mg 2 - 4 times daily [17].

Our analyses of recommendations presented chronologically provide comprehensive evidence of the comparative interchangeable efficacy of high and low doses of PPI therapy in managing patients with UGIB after successful endoscopic treatment; however, it remains hard to determine the most appropriate PPI regimen for intermittent PPI therapy due to variation of low dose regimens in studies included in meta-analyses.

4. Discussion

Current data is controversial. For example, a study by Hung *et al.* [18] has shown that intermittent intravenous (IV) PPI dosing matches the efficacy of continuous PPI administration. However, contrasting outcomes were observed in other studies, such as those by Khan *et al.* [19], which reported inferior results with IV bolus PPI therapy compared to continuous infusions in peptic ulcer bleeding patients, particularly those with high-risk features.

The prevailing hypothesis for utilizing high-dose Proton Pump Inhibitor (PPI) therapy in patients with bleeding ulcers is based on in vitro studies. It states that using PPI is associated with a significant shift in the gastric environment, promoting mucosa healing, blood clot formation, and stabilization. However, despite the short half-life of PPIs (approximately 1 hour), their binding to the acid pump results in irreversible inhibition of acid secretion [7] [8] [18] [19] [20] [21] [22].

By summarizing above the data of our analysis, we see how recommendations regarding high vs. low PPI regimen changed over time: from no difference in re-

gimen in 2010 [12] to recommending continuous regimen in 2012 [13] to declaring insufficient evidence between choosing one regimen over another in 2013 [14] to determine that both regimens are comparable to each other in 2014 [15] and 2018 [16] and finally to recommending both regimens in 2021 [17].

To conclude, our review of available data from 5 meta-analyses and systematic reviews shows that in patients with bleeding ulcers and high-risk endoscopic findings, intermittent PPI therapy is non-inferior to the currently recommended regimen of intravenous bolus plus continuous infusion of an intravenous PPI for 3 days, 7 days bleeding risk or mortality; however, it remains hard to determine the most optimal intermittent regimen due to different PPI regimens in low dosage groups, as well as the heterogeneity and bias portion of RCTs included in meta-analyses. Further research and meta-analyzes with a standardized dose and type of PPI selection and proper stratification of patients based on the severity of bleeding and endoscopic findings are required.

5. Conclusions

Based on available meta-analysis data and the latest ACG recommendations, our analysis shows that an intermittent PPI regimen is comparable to continuous therapy after successful treatment of upper gastrointestinal bleeding (UGIB) while being cost-effective at the same time.

According to the results of our analysis, we recommend substituting a continuous PPI regimen with similarly effective intermittent PPI therapy to decrease total PPI dose, cost, and resource use while maintaining quality and safety of care in patients with acute UGIB after endoscopic intervention.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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