A Comparison between the Impacts of Continuous and Intermittent Intravenous Pantoprazole Injection on High Risk Upper Gastrointestinal Bleeding

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ABSTRACT

Background & Objective: Although higher age was previously associated with upper gastrointestinal bleeding (UGIB), rebleeding due to low PH has been recently considered as a crucial prognosis factor. In this regard, pantoprazole, a Proton pump inhibitor (PPIs), along with endoscopy was applied in high-risk patients. As it is an undeniably momentous approach to discover the best PPIs injection method, the advantages and disadvantages of continuous and intermittent PPIs' infusion were compared in high-risk UGIBs patients.

Materials & Methods: Eighty selected patients were randomly divided into two equal groups. In the continuous infusion, there were 6 and 34 patients with adherent clot ulcers and visible vessel ulcers without bleeding; however, 2 and 38 patients with these ulcers were present in the intermittent infusion group in turn. After three days, ulcers, packed cells, and surgery needs were evaluated between the two groups.

Results: After 72 hours of treatment, 29, 3 and 8 patients in the continuous group showed clean base, flat pigmented spot, and visible vessel ulcer with bleeding, respectively. Whereas in the intermittent group, these records were 35, 5 and 0, respectively ($p \leq 0.028$). The number of patients in the continuous infusion group with a visible vessel ulcer was significantly higher (p>0.028). A significant difference was also observed between the groups in terms of length of hospitalizations ($p \leq 0.001$) with no mortality.

Conclusion: Based on the findings, the intermittent infusion of PPIs is obviously superior over continuous mode. However, further studies with a larger population are recommended to discover the merits and drawbacks of this method in high-risk UGIBs.

Keywords: Upper gastrointestinal bleeding, Proton pump inhibitors, Continuous infusion, Intermittent infusion.

Introduction

Upper gastrointestinal bleeding (UGIB) is a serious medical condition requiring prompt and effective management. Rebleeding is one of the most critical factors contributing to mortality and morbidity in UGIB patients. Rebleeding occurs when bleeding resumes after initial treatment or intervention. It can worsen the patient's condition and increase the risk of complications. However, advancements in medical technologies and the implementation of advanced endoscopic procedures have played a crucial role in improving outcomes for UGIB patients. These procedures enable more precise identification and treatment of the bleeding source, thus, decreasing the mortality (from 4.5% to 2.1%) and hospitalization (down 20%) rates **(1-6)**. Although this technique alone can bring successfully hemostasis in more than 90% of these patients, rebleeding still occurs in approximately 10-30% of the cases **(7)**. Gastric acidity can be considered the most significant pathogenesis reason by interfering with coagulation pathways, through

digesting clot at acidic PH, or platelet aggregations adversely. Proton pump inhibitors (PPIs) can serve as an antagonist of H 2-receptor, a modifier of gastric acid secretion to address this issue **(8-11)**.

Despite promising outcomes of PPIs, there is no consensus on the optimal administration and dose in patients with UGIB. High-dose continuous infusion involves a bolus injection of PPI followed by a continuous infusion at a higher rate. The goal is to achieve and maintain a more consistent and prolonged effect on gastric acid suppression. This method aims to provide enhanced clot stability and reduce the risk of rebleeding. On the other hand, intermittent PPI therapy involves the use of PPIs in standard intermittent doses, such as once or twice a day. Some studies have shown that this approach can be equally safe, effective, and cost-effective in treating UGIB compared to continuous infusion. **(7, 12)**. Other studies have found no significant differences between these two methods in treating UGIB. Therefore, the choice between these two methods is not always straightforward, and there is no definitive consensus on the superiority of these approaches **(7, 13-15).**

Based on endoscopic stigmata of recent hemorrhage, patients can be categorized into four groups: clean base ulcer, flat pigmented spot ulcer, adherent clot ulcer, and visible vessel ulcer with or without bleeding. The latter two have a higher probability of rebleeding, surgery, and PPI therapy. Therefore, this study considered these classes to determine better therapeutic techniques for preventing adverse outcomes of high-risk UGIB **(14-16).**

The present clinical trial study aimed to compare the effectiveness of continuous and intermittent infusion of PPIs in reducing the need for packed cells, urgent surgery, hospitalization, and preventing rebleeding simultaneous with endoscopy in high-risk UGIB.

Materials and Methods

Data Collection

Among patients referred to the hospital in the second half of 2018, eighty patients were selected. Exclusion criteria included pregnancy or active bleeding during treatment, flat pigmented spot ulcer, clean base ulcer, tumoral ulcer, and bleeding varices. While the inclusion criteria included the age range of 18-80, having no obvious upper gastrointestinal bleeding (Including Hematemesis, Melena, and Hematochezia) with the visible vessel, adherent clot, and red spot in endoscopy. These patients were successfully treated with adrenaline injection during endoscopy, or they received thermal therapy with bipolar electrocoagulation or heater probe.

Study procedures

Using the coin the Flip randomized method, the patients were randomly divided into two groups based on the period of pantoprazole's infusion; the intermittent (40 mg per 8 h) and continuous (8 mg per h) groups. After obtaining the ethics committee approval (ethic number: IR.ZUMS.REC.1398076) and informed consent, the patients were treated and followed up for three days. On the third day, all patients underwent upper endoscopy. It should be noted that hemodynamically unstable patients (systolic blood pressure less than 90 mm Hg or tachycardia with a heart rate above 120 beats per minute), first stabilized with appropriate fluid therapy and then considered.

Reperfusion and a shift from high-risk to low-risk bleeding ulcers were considered to assess primary outcomes within three days after endoscopic treatment. More precisely, a treatment failure was defined as the presence of bleeding and ulcers (except clean or pigment ulcers). Besides, the groups were compared in terms of the length of hospital stay, packed cell requirements, bleeding-induced mortality, and need for surgery.

Sample size calculation and statistical analysis

The formula $n=\frac{\left[Z_{1-\frac{\alpha}{2}}+Z_{1-\beta}\right]^2[\delta^2]}{(\mu 1-\mu 2)^2}$ was applied to evaluate the sample size. Data analysis was conducted using SPSS 16.0 (SPSS Japan, Tokyo). To compare mean values between two groups, independent t-test and the Mann-Whitney test were used for data with normal and skewed distribution, respectively. The Chi-square test was utilized to determine the relationship between qualitative and nominal variables. Nagelkerke's R squared was employed to evaluate the goodness of fit of the logistic regression model which implies the power of explanation of the model. To eliminate the effects of intervening variables, multivariate statistics (ANOVAs) were applied. A P-value ≤ 0.05 was considered significant.

Results

Baseline and clinical features upon arrival at the hospital

In this study, 80 patients with a risk of UGIB were randomly divided into two equal groups based on the type of infusion (continuous or intermittent). The mean age ± SD of the patients in the continuous and intermittent intravenous infusion of pantoprazole groups was 52.87±13.78 and 48.87±13.68, respectively; showing no significant differences ($p> 0.107$). At admission time, 17 patients in the continuous group had stable hemodynamic status while 23 had unstable; these rates were 16 and 24 patients in the intermittent group, respectively. Similarly, the two groups showed no statistically significant differences ($p> 0.820$). Moreover, based on the type of ulcers observed in endoscopy, six patients had adherent clot ulcers, but 34 patients had visible vessel ulcers without bleeding in the continuous infusion group. Nonetheless, there were two individuals with adherent clot ulcers and 38 with visible vessel ulcers without bleeding in the intermittent group. In this respect, the

groups had no significant difference (*p> 0.136*). Overall, in this study, there was no red spot after primary endoscopy.

Ulcer appearance and Hospital stay after 72 hours of therapy

Within the interval, in the continuous infusion group, 29, 3, and 8 patients had clean base ulcers, flat pigmented spot ulcers, and visible vessel ulcers with bleeding, respectively. On the other hand, the intermittent group exhibited 35 clean base ulcers and five flat pigmented spot ulcers with no visible vessel ulcer with bleeding. The visible vessel ulcer with bleeding in the continuous infusion group (with eight patients) was notably more than the intermittent group (*p-value > 0.028*). Likewise, the mean length of hospitalization in the continuous infusion group (5.45 ± 2.55 days) was significantly longer than the intermittent group (4.92 ± 0.92 days) (P-value >0.0001) (Table1).

Table1. Variables in two groups after 72 hours of hospitalization

		Continuous pantoprazole infusion group n=40 (100.0 %)	Intermittent pantoprazole infusion group n=40 (100.0%)	P-value
Ulcer appearance	Clean base	29 (73)	35 (88)	0.028
	Flat pigmented spot	3 (7)	5 (12)	
	Visible vessel with bleeding	8 (20)	0 (0)	
Mortality		0	0	-
Packed cell infusion		28	28	1.000
Hospitalization's length (mean)		5.45 ± 2.55	4.92 ± 0.92	0.0001
surgery		3	0	0.077

According to Table2, logistic regression showed no significant difference in ulcer appearance three days after treatment between the two groups. On the contrary, regarding the length of hospitalization, patients treated with the intermittent method were 11.9 % less hospitalized than those treated by the continuous infusion approach.

Table2. Calculation of ulcer appearance regression and length of hospital stay 3 days after treatment

	Nagelkerke R^2	P-value
Ulcer appearance	0.183	0.835
Hospitalization's length	0.119	0.03

Transfusion and surgery after 72 hours of therapy

The studied groups showed no difference concerning the need for packed cell infusion or urgent surgery which can be assigned to similar prevalence of packed cell infusion (28 patients per group), as only three patients were in urgent need for surgery in the continuous infusion group (*p-value >0.077*). Yet there was no mortality in either groups (Table1).

Discussion

To the best of the authors' knowledge, this is the first clinical study addressing a comprehensive evaluation of continuous and intermittent infusion of proton pump inhibitors (PPIs), pantoprazole, in patients with upper gastrointestinal bleeding. The results revealed distinct effects of a combination of intermittent infusion technique with endoscopic homeostasis on UGIB prognosis.

The two groups exhibited no significant difference in mean age (52.87±13.78 and 48.87±13.68 for the continuous and intermittent infusion groups, respectively). Likewise, hemodynamic status and wound type had no impact on the results during endoscopy.

A meta-analysis by Grigoris et al. showed in that PPIs lessen the overall rebleeding in patients with ulcer bleeding even though they did not separate patients into two groups to compare which injection technique is more effective **(19)**. This research showed a significant difference in the appearance of ulcer by dividing them into two groups based on the infusion method: One fifth of those who received PPIs via the continuous infusion had visible vessel ulcers with bleeding, while none of those treated with intermittent injection showed visible vessel ulcers with bleeding. However, our results were in contrast with Yüksel İ and Serpico M et al.; who reported that the method of PPIs therapy had no meaningful effects on the prevalence of rebleeding in patients with active peptic ulcers. In their study, the amount of pantoprazole for the continuous and intermittent infusion was 8mg/h and 40mg/12h, respectively. Similarly, the results of the Yamada et al. were in line with the Yüksel study **(7,14,20).** Furthermore, Sachar H et al. studied intermittent PPI therapy in high-risk ulcer bleeding and concluded that this approach is more cost-effective and leads to lower rebleeding than continuous therapy **(15)**. Therefore, the aforementioned infusion probably varies depending on the quality and dosage of the drug (herein 40mg/8h pantoprazole) and the occurrence of bleeding (herein upper gastrointestinal). Considering the similarity of these studies to the present research and the primary role of rebleeding in mortality, our findings suggest a promising approach to determine the optimal dose of the intermittent PPI with proper effectiveness on these patients in the future.

Reports from clinical studies such as Yüksel İ et al., unveiled the equal efficacy of continuous and intermittent PPIs in the number of packed cell infusions (2.18 and 2.59 units in turn) and urgent surgeries (2 patients in each category) for patients with GI bleeding **(7)**. Another study by Serpico M, however, did not find any effectiveness of PPIs therapy on reducing packed cell transfusions or emergency surgery **(20)**. Our study aligns with these findings, making intermittent treatment more preferable due to its cost-effectiveness and shorter duration.

The duration of hospital stay was another subtle analogy in our study due to its economic burdens on the patients. Yüksel İ et al. found that the intermittent infusion was non-inferior to the continuous (4.17±1.72 and 4.41±1.82 in turn**(7)**. We observed a significant discrepancy between these groups in this regard: the length of hospitalization with the continuous method was 5.45 ± 2.55 days, while it was 4.92 ± 0.92 days for the intermittent method —11.9% less than the continuous one. Unlike the findings of the current research, in the mentioned study, the patients were treated by PPIs after endoscopic treatment to prevent further consequences, and patients with severe bleeding from visible vessels also were included.

The mortality rate was another contributory factor when it comes to a comparison between these two different methods of injection. Our results demonstrated no death during treatment in both groups, similar to the previous studies by Yüksel İ et al. and Serpico M et al. **(7, 20).**

Conclusion

According to the findings of this study, the intermittent infusion of PPI significantly reduces the risks related to the length of hospitalization and rebleeding compared to continuous infusion. Despite some discordance about the impacts of these techniques on surgical intervention and packed cell infusions, the number of surgery was lower in the intermittent method. Besides, the endoscopic appearance of ulcers was also more stable with intermittent therapy. Given the higher burden of continuous infusion on patients and medical staff, the intermittent intravenous injection of PPIs seems to be preferable for UGIB. Further studies with larger populations are necessary to deeper understanding of the efficiency of the intermittent therapy in reducing packed cell infusions and urgent surgeries.

Main Points

- The intermittent infusion of PPI notably reduced the length of hospitalization and rebleeding while continuous one did not.
- The intermittent infusion of PPI was significantly much more cost-effective than continuous infusion.
- The two methods showed no difference in packed cell consumption and urgent surgery requirement.

- Interestingly, none of the techniques had mortality.

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Authors' Contributions

FM , SJ conceptualized and designed the study. Data collection:MN Clinical Process:SJ All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

The study was approved by Zanjan University of medical science local ethics committee (Approval Date: 18 April 2019, Approval Number: IR.ZUMS.REC.1398076).

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