



## Comparison of Oral versus Intravenous Proton Pump Inhibitors in Preventing Re-bleeding from Peptic Ulcer after Successful Endoscopic Therapy

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### ABSTRACT

#### BACKGROUND

Proton pump inhibitors (PPIs) are now widely prescribed for the management of patients with acute upper gastrointestinal bleeding; although its optimal dose and route of administration has remained a controversial issue. The aim of this study was to assess the clinical effectiveness of high dose oral versus intravenous (IV) PPI after successful endoscopic therapy in patients with bleeding peptic ulcer disease.

#### METHODS

178 patients with active upper gastrointestinal bleeding due to a peptic ulcer with stigmata of high risk for re-bleeding entered the study. After successful endoscopic hemostasis, they were randomized to receive either high dose oral pantoprazole (80 mg stat and 80 mg twice daily for 3 days) or high dose intravenous pantoprazole (80 mg IV infusion within 30 minutes and 8 mg per hour for 3 days). After the 3rd day, the patients in both groups received oral pantoprazole 40 mg twice daily for one month. The end points were comparing the rate of re-bleeding or mortality, and the need for blood transfusion or surgery during the first month between the two groups.

#### RESULTS

There were not significant statistical differences between the two groups in the volume of blood transfusion, mean duration of hospital stay, need to surgery, or mortality rates. However, the rates of re-bleeding were 2.3% (2:88) in the IV group and 3.3% (3:90) in the oral group ( $p = 0.6$ ).

#### CONCLUSION

According to our findings, it seems that high dose oral PPI can be a good alternative to high dose IV PPI in patients with bleeding peptic ulcer who are at high risk of re-bleeding. Due to the lower cost and the availability of oral PPIs, their use can be economically much more affordable.

#### KEYWORDS:

Proton pump inhibitor, Peptic ulcer, Hemorrhage, Endoscopic therapy

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### INTRODUCTION

Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding (UGIB), accounting for about 50% of cases.<sup>1,2</sup> In a recent review article from Iran peptic ulcer disease was the most common cause of UGIB (30-65%) and erosive gastro-duodenopathy ranked the second (16-25%).<sup>3</sup> It remains a serious medical problem with significant morbidity and mortality. Endoscopic therapy significantly reduces further bleeding, surgery, and mortality in patients with bleeding peptic ulcers and is now recommended as the first hemostatic modality for these patients.<sup>4-6</sup> However, there is a high risk of



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peptic ulcer re-bleeding in 14-36% of patients in spite of efficient endoscopic intervention.<sup>7,8</sup>

Gastric acid inhibits clot formation and promotes clot lyses and accordingly, disturbs hemostasis of ulcers in the stomach and duodenum.<sup>9</sup> Therefore, reduction of gastric acid secretion can prevent ulcer re-bleeding.<sup>8</sup> Proton pump inhibitors (PPIs) are the drugs that are widely used to reduce gastric acid secretion. Intravenous (IV) and oral pantoprazole with equal dose have similar acid suppression effect.<sup>10</sup> Compared to standard dose of oral PPI, high dose oral PPI has faster acid suppression<sup>11</sup> and also high dose IV PPI has faster adequate acid suppression effect (gastric acid PH > 6) than high dose oral PPI.<sup>11,12</sup> However, the optimal route, dose, and duration of PPI therapy after endoscopic therapy of a bleeding peptic ulcer remain controversial.

Several controlled trials and meta-analyses have shown the comparable efficacy of IV and oral PPIs in ulcers at high risk of re-bleeding after endoscopic therapy. However, they mostly recommended further studies to confirm the results.<sup>13-17</sup>

In this study, we attempted to evaluate and compare the effects of IV and oral PPIs in preventing re-bleeding from peptic ulcers after successful endoscopic therapy.

## MATERIALS AND METHODS

### Design and patients:

This study was a single center, prospective, randomized trial conducted in a tertiary teaching hospital (Imam Khomeini Hospital, Sari) in Iran. The protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences and was also registered in Iranian Registry of Clinical Trials (number: IRCT2014082515510N2). Furthermore, a written informed consent was obtained from all subjects.

From June 2014 to May 2015, all adult patients who were admitted to our Gastroenterology Department with symptoms of UGIB, as documented by hematemesis, melena, or hematochezia, were considered to be included in this study. They were evaluated by upper GI endoscopy during the first 24 hours of admission, after hemodynamic stabilization. It should be mentioned that all patients received IV pantoprazole (80 mg stat followed by 8 mg infusion per hour) before endoscopic assessment.

Patients older than 18 years with successful endoscopic therapy of high risk ulcers for re-bleeding [defined as

spurting bleeding (Forrest IA), oozing bleeding (Forrest IB), non-bleeding visible vessel (Forrest IIA) or adherent clots (Forrest IIB)] were enrolled in the study.<sup>18</sup> On the other hand, patients with low risk of bleeding from ulcers (clean base ulcer, flat pigmented ulcers), suspicious malignant ulcer, bleeding tendency, uremia, liver cirrhosis, and Mallory Weiss tear were excluded from the study.

Therapeutic endoscopy for patients with high risk peptic ulcer for bleeding (Forrest IA-IIB) were done by injecting up to 40 mL of epinephrine (diluted 1:10000) around the ulcer crater to stop bleeding and electrocoagulation therapy by Argon Plasma Coagulation (APC) for all patients. Also, a biopsy sample was taken from antrum for evaluating *H. pylori* infection. For patients with unsuccessful endoscopic therapy, an immediate surgery consultation was performed.

The enrolled patients were randomly allocated into two groups using sealed envelopes containing a therapeutic option (either IV or oral pantoprazole). In the oral pantoprazole (Oral-Pan) group, the patients received pantoprazole (Nolpaza, Iranian pharmaceutical company Actoverco) 80 mg orally early after endoscopy and then twice daily for 72 hours. In the IV pantoprazole (IV-Pan) group, the patients received injective pantoprazole (Pepti care, Iranian Razak Drau Company) 80 mg, infused during 30 minutes and then 8 mg/hour IV pantoprazole for 72 hours. After the 3rd day, all the patients of both groups received oral pantoprazole 40 mg twice daily.

During the hospital stay, the serum hemoglobin (Hb) was checked every 8 hours. Blood transfusions were performed if Hb was lower than 7 g/dL in young patients or lower than 9 gr/dL in patients older than 50 years or in patients with history of ischemic heart disease (IHD) or those being in shock. After endoscopic therapy, re-bleeding was suspected if hematemesis reappeared or the patient developed orthostatic hypotension, unstable vital signs (systolic blood pressure < 90mmHg, pulse rate > 120/min) or Hb drop > 2g/dL (despite blood transfusion). Patients suspected to re-bleeding underwent urgent endoscopy and if active bleeding, fresh blood, or blood clots were seen, epinephrine injection and APC were performed. Then they again received pantoprazole according to their protocol group. Also, in case of definite cardiac or neurological indications for continuing Aspirin intake, the drug was given to the patients after 24 hours

**Table 1: Demographic and clinical variables of patients at entry to the study**

| Variable                | IV PPI group | Oral PPI group | P value |
|-------------------------|--------------|----------------|---------|
| Number of patients (%)  | 88 (49.4%)   | 90 (50.6%)     | 0.9     |
| Mean age (Years)        | 60.3 (25-89) | 58.4 (18-100)  | 0.8     |
| Sex:                    |              |                |         |
| • Male                  | 49 (55.7%)   | 63 (70%)       | 0.04    |
| • Female                | 39 (44.3%)   | 27 (30%)       |         |
| Smoking                 | 22 (25%)     | 29 (32.2%)     | 0.3     |
| History of PUD          | 14 (15.9%)   | 9 (10%)        | 0.2     |
| Aspirin or NSAID        | 68 (77.2%)   | 63 (60%)       | 0.4     |
| Clopidogrel             | 7 (8%)       | 4 (4.4%)       | 0.3     |
| Warfarin                | 7 (8%)       | 2 (2.2%)       | 0.9     |
| Melena                  | 69 (77.3%)   | 77 (85.6%)     | 0.3     |
| Hematemesis             | 51 (57.7%)   | 38 (42.2%)     | 0.5     |
| Mean initial Hb (gr/dL) | 9            | 8.7            | 0.8     |
| Mean supine BP (mm Hg)  | 113/72       | 112/70         | 0.9     |
| Mean sitting BP         | 111/71       | 109/69.5       | 0.8     |

NSAID: non-steroidal anti-inflammatory drug; Hb: Hemoglobin, BP: Blood pressure; PPI: proton pump inhibitor; PUD: peptic ulcer disease

**Table 2: Endoscopic findings of the patients in the two groups**

| EGD Findings                | IV-Pan group | Oral-Pan group | P value |
|-----------------------------|--------------|----------------|---------|
| Gastric ulcer               | 39           | 36             | 0.5     |
| Duodenal ulcer              | 57           | 59             | 0.9     |
| Adherent clot               | 26 (29.5%)   | 18 (20%)       | 0.14    |
| Oozing                      | 23 (26.1%)   | 33 (36.7%)     | 0.13    |
| Non-bleeding visible vessel | 38 (42.2%)   | 38 (42.2%)     | 0.8     |
| Spurting                    | 1 (1.1%)     | 1 (1.1%)       | 0.9     |

EGD: Esophagogastroduodenoscopy

of endoscopic treatment.

On the day of discharge, a standard *H. pylori* eradication regimen followed by oral PPI (pantoprazole 40mg twice daily) was prescribed for patients infected with *H. pylori*, but the rest of the patients were advised to continue just oral PPI for one month. They were all asked to be visited at the end of one month or sooner in case of any problem.

A questionnaire including demographic characteristics, history of previous UGIB, non-steroidal anti-inflammatory drugs (NSAIDs) or Aspirin use, volume of blood transfusion at entry and during hospital stay, the days of hospital stay, endoscopic findings, and the need for re-endoscopy, and surgery, and mortality rates up to one month after discharge were completed for all patients.

Statistical analysis was performed using SPSS software (version 16, Chicago, IL, USA). The descriptive variables such as mean, standard deviations, and frequency were used. Chi square (X<sup>2</sup>) and t tests were used as appropriate. P value less than 0.05 was considered as statistically significant.

## RESULTS

From June 2014 to May 2015, 376 patients with clinical evidence of UGIB were admitted to our hospital. Upper GI endoscopy was performed for all patients. 178 patients had endoscopic evidence of high risk peptic ulcers for re-bleeding (according to Forrest classification). They underwent therapeutic endoscopy, using diluted adrenaline injection and APC. Also, in two patients, clips were used to control bleeding. These high risk patients were enrolled in the study; 88 patients were randomly allocated to the IV-Pan group and 90 patients were allocated to the oral-Pan group.

The causes of GI bleeding in the remaining 198 patients were esophageal varices, clean-base ulcers, esophageal cancer, Mallory Weiss tearing, gastric cancer, and Dieulafoy's lesion. They were excluded from the study.

All the patients completed the study. 112 patients were men (63%) and 66 patients (37%) were women. Other demographic and also clinical and endoscopic data are shown in tables 1 and 2.

**Table 3: Primary and secondary outcomes in the two groups**

| Outcome   | IV-Pan group | Oral-Pan group | P value |
|---|--------------|----------------|---------|
| Mortality (%)                                     | 3(3.4%)      | 1 (1.1%)       | 0.3     |
| Re-bleeding (%)                                   | 4 (4.5%)     | 3 (3.3%)       | 0.6     |
| Surgery (%)                                       | 1 (1.1%)     | 1 (1.1%)       | 0.9     |
| Volume of blood transfusion (unit of packed cell) | 113          | 117            | 0.8     |
| Mean duration of hospital stay (Days)             | 3.7          | 3.4            | 0.8     |
| Repeated EGD                                      | 5 (5.6%)     | 3 (3.3%)       | 0.6     |

EGD: Esophagogastroduodenoscopy

Seven patients (3.9%) re-bled. Four patients were in the IV-Pan group and three were in the Oral-Pan group. Four of the re-bleedings happened during hospital stay and three happened at the 8<sup>th</sup>, 8<sup>th</sup>, and 15<sup>th</sup> day after hospital discharge, respectively. There were no significant differences between the two groups in the rate of re-bleeding, neither during hospital stay, nor after discharge (table 3).

Accordingly, eight patients needed second endoscopy; five were in the IV-Pan group and three were in the oral-Pan group ( $p = 0.6$ ). The reason for the repeated endoscopies were re-bleeding in seven patients (as mentioned previously) and second-look endoscopy to assess the quality of the performed injection and APC in one patient.

Two patients underwent surgery during hospital stay. One was in the IV-Pan group and the other was in the Oral-Pan group. The first patient underwent surgery at the first day of hospital admission and the second patient underwent surgery at the second day due to re-bleeding. The reason for surgery was the inability of therapeutic endoscopy to control the bleeding.

Four patients died; three patients were in the IV-Pan and one in the Oral-Pan group, respectively (table 3). Three patients died at presentation due to massive GIB that could not be controlled endoscopically and they died before undergoing surgery. But the 4<sup>th</sup> patient underwent surgery and died at the 11<sup>th</sup> day after surgery. All the patients were older than 60 years.

For all the patients oral feeding was started 24-48 hours after successful therapeutic endoscopy and they were discharged from hospital if they had stable vital signs and acceptable hemoglobin levels. After discharge, all the patients were followed up by phone call contacts up to one month to ask about re-bleeding, hospital re-admission, blood transfusion, surgery, and mortality.

## DISCUSSION

According to the results of our study, there were no significant differences between the two groups of IV-Pan and Oral-Pan in the rates of re-bleeding and re-endoscopy, duration of hospital stay, the volume of blood transfusion, and rates of surgery and mortality during one month of follow up. There are several other studies that have shown almost the same results.

In 2008, Tsai and colleagues conducted a study in which 156 patients with high risk peptic ulcers were divided into two groups to receive either IV PPI or oral PPI for the first 72 hours after therapeutic endoscopy. Afterwards, all the patients received standard doses of oral PPI. The outcomes of re-bleeding, need to transfusion, mortality, surgery, and duration of hospital stay were similar in both groups.<sup>19</sup>

Also, in 2011, Mostaghni and co-workers showed no significant differences in the rate of re-bleeding, duration of hospital stay, and the volume of blood transfusion among 85 patients with high risk peptic ulcer disease who had received either high dose oral omeprazole or IV pantoprazole during the first 72 hours after therapeutic endoscopy.<sup>15</sup>

In 2012, Yen and others evaluated the adverse outcomes of PUD bleeding in 100 patients who had been divided into two groups of high dose IV and oral PPI after therapeutic endoscopy. They showed that duration of hospital stay was shorter in oral PPI group (1.8 days vs. 3.9 days, respectively), but the difference was not statistically significant. Also, other outcomes of GIB including the rates of re-bleeding, surgery, mortality, and volume of transfusion were similar in both groups.<sup>14</sup>

In another single-center, randomized, controlled, double-blind and double-dummy study in 2014, 244

patients with bleeding PUD, entered the study after therapeutic endoscopy. 118 patients received high dose IV esomeprazole plus oral placebo, and 126 patients received high dose oral esomeprazole plus placebo IV infusion for 72 hours. The patients were followed up for 30 days after index bleeding. According to the results, no difference existed between the two groups in outcomes of re-bleeding, need to blood transfusion, days of hospital stay, and re-endoscopy. However, this study stopped prematurely and therefore, the results of the study are not conclusive for equivalency or non-inferiority of two treatment regimens.<sup>16</sup>

In 2013, Tsoi and colleagues performed a meta-analysis to compare the outcomes of administering oral versus IV PPI after therapeutic endoscopy in patients with high-risk PUDs. Six randomized clinical trials from 2006 to 2011, including 615 patients, (302 patients in oral PPI and 313 patients in IV PPI groups) were evaluated. The outcomes of re-bleeding, volume of blood transfusion, need for surgery, days of hospital stay, and all-cause mortality showed no statistically significant differences between the two groups.<sup>17</sup>

Finally, according to two recent systematic reviews and meta-analyses, both oral and IV PPI can be effectively used after endoscopic treatment of high risk ulcers.<sup>20,21</sup>

Although our results are almost similar to previous studies, our study had a limitation. The endoscopies had been performed by six gastroenterologists. This might have interfered with the same interpretation of the ulcers. However, we used Forrest classification in order to standardize the interpretation of the ulcers. On the other hand, using Iranian brand of pantoprazole is a strong point of our study.

In conclusion, our study showed no statistically significant difference between the two groups of IV or oral PPI in the outcomes of high risk peptic ulcers after therapeutic endoscopy. Therefore, it seems that high dose oral PPI can be a good alternative to high dose IV PPI in patients with bleeding peptic ulcer disease. Furthermore, due to the lower cost (approximately 30 times) and availability of oral PPI, its use can be economically much more affordable. We suggest further studies to evaluate the effects of different types of oral PPIs on the outcomes of high risk peptic ulcers after therapeutic endoscopy.

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#### ETHICAL APPROVAL

There is nothing to be declared.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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