Original Article

Comparison of oral and intravenous proton pump inhibitor in patients with high risk bleeding peptic ulcers

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Objective: To compare the efficacy of oral omeprazole vs intravenous omeprazole in decreasing risk of re-bleeding in peptic ulcer patients.

Methodology: This prospective, randomized, controlled clinical trial was conducted at Ghulam Mohammad Mahar Medical College Hospital, Sukkur, Pakistan from January 2010 to December 2011. One hindered and six patients with high risk peptic ulcer were randomized to receive either oral omeprazole (80mg BID for 3 days) or IV omeprazole (80mg bolus and 8mg/hour infusion for 3 days) followed by omeprazole (20mg each day for 30 days). All patients underwent upper endoscopy and endoscopic therapy within 24 hours.

Results: Seventeen patients were excluded from the study. Forty four patients were randomly allocated into oral omeprazole group and 41 to IV omeprazole group. Both groups were similar for factors affecting the outcome. Bleeding reoccurred in five patients of oral omeprazole group and four patients in IV omeprazole group (11.4% vs 9.8%). The mean hospital stay and blood transfusion were not different in both groups.

Conclusion: Oral omeprazole and IV omeprazole had equal effects on prevention of re-bleeding after endoscopic therapy in patients with high risk bleeding peptic ulcers. (Rawal Med J 2013;38:7-10).

Keywords: Oral PPI, IV PPI, bleeding peptic ulcer.

INTRODUCTION

Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding accounting for about 50% of episodes.[1,2] Endoscopic therapy of high risk ulcers such as epinephrine injection reduces re-bleeding, morbidity and even mortality.[3,4] Therefore, it is currently recommended as the first line of haemostatic intervention for these patients.[4,5] However, high risk ulcers re-bleed in 14-36% of patients in spite of efficient endoscopic intervention.[5,6] Gastric acid inhibits clot formation and promotes clot lyses and, therefore disturbs homeostasis of ulcers in the stomach and duodenum. Thus, reduction of gastric acid secretion could prevent ulcer re-bleeding.

Several controlled trials and meta-analyses have shown the efficacy of intravenous and oral proton pump inhibitors (PPIs) in high risk bleeding ulcers after endoscopic therapy.[7-13] The comparable effectiveness of oral (PO) and intravenous (IV) route of administration is not well known; therefore a few cost-effectiveness studies were designed, but they showed conflicting results and were not conclusive.[14-17] Comparing oral and IV administration of PPI in bleeding peptic ulcers has been studied, however, some problems were encountered in these studies.[17,18] Bajaj et al. has done a pilot study with small number of patients and Tsai et al. had used regular dose and not high dose of PPI.[21,22] The aim of this study, therefore, was to compare oral and intravenous high dose of PPI in high risk peptic ulcer bleeding after endoscopic intervention.

METHODOLOGY

The protocol was approved by hospital Ethics Committee and a written informed consent was obtained from all participants. From January 2010 to December 2011, all adult patients who were admitted via emergency department to Medical Unit-I of Ghulam Mohammad Mahar Medical College hospital Sukkur, Pakistan with hematemesis, melena or hematochezia were considered for inclusion in the study. Endoscopy was performed within 24 hours after admission. Patients older than 18 years with successful

endoscopic therapy of high risk ulcers [defined as active bleeding (Forrest IA, IB), non-bleeding visible vessel (NBVV, Forrest IIA) or adherent clots (Forrest IIB)] were enrolled. Patients with low risk ulcers (clean base, ulcers with a simple washable clot), suspicious malignant ulcer, bleeding tendency, uremia, liver cirrhosis, Mallory Weiss tear or already on PPI as an outpatient were excluded from study.

All were managed endoscopically by injecting 5-30 ml of epinephrine (diluted 1:10000) around the ulcer crater. Cavitations or flattening of bleeding vessel and disappearance of NBVV was considered as established homeostasis. A biopsy was taken from antrum for evaluating *Helicobacter pylori* infection. Patient with unsuccessful endoscopic therapy were not enrolled and were referred to general surgeon. Information on demography, history of previous upper gastrointestinal bleeding, NSAID or ASA ingestion, ulcer location, bleeding stigmata and blood transfusion volume at entry were recorded in all patients.

Enrolled patients were allocated into two groups based on even and odd days of the month. In the oral omeprazole (PO-OMP) group, the patients received 40 mg omeprazole orally twice daily for 72 hours. In IV omeprazole (IV-OMP) group, they received Inj. Omeprazole 80 mg bolus and then 8 mg/hour infusion for 48-72 hours. Then, all patients received omeprazole 20 mg orally for 30 days. On the day of discharge *H. pylori* infected patients received standard regimens.

The Hemoglobin (Hb) was checked every 8 hours and blood transfusion was done if it was lower than 8g/dl or if patient was in shock. Re-bleeding was suspected if persistent tarry stool, reappearance of hematemesis, orthostatic hypotension, unstable vital sign (BP≤90 systolic, PR≥120) or Hb drop ≥2 g/dl, (despite blood transfusion) developed after the first endoscopic therapy. Patients suspected to re-bleeding underwent urgent endoscopy and if active bleeding, fresh blood or blood clots were seen, epinephrine injection was performed.

Statistical analysis was performed using SPSS V 11.5. Chi Square (X^2) was performed for finding out the association between re-bleeding, blood transfusion, re-endoscopy and PO-OMP or IV-OMP groups. T-test was used to determine difference between hospital stay, amount of blood transfusion and PO-OMP or IV-OMP groups. $P<0.05$ was considered significant.

RESULTS

Out of 209 patients with upper GI bleeding, 102 had high risk peptic ulcer on endoscopic evaluation. Seventeen patients were excluded from the study (bleeding tendency=4, uremia=2, gastric cancer=3, Mallory Weiss tear=1, esophageal varices=4, primary endoscopic failure=3). Finally, 85 patients completed the study (44 patients in PO-OMP group and 41 patients in IV-OMP group). Both groups were similar in source of bleeding and factors affecting the out-come (Table 1).

Table 1: Demographic and clinical characteristics of study population (n=89).

	PO-OMP group (n=44)	IV-OMP group (n=41)
Gender (male/Female)	33/11	30/11
Age(years) (mean ±SD)	57.25±16.45	61.66±17.17
NSAID, ASA use (%)	19 (43)	17(41)
Ulcer Location		
Gastric (%)	24(54)	18(44)
Duodenal (%)	17(39)	20(49)
Both (%)	3(7)	3(7)
Ulcer stigmata		
Adherent clot (%)	5(11)	3(7)
Visible Vessel (%)	25(57)	26(63)
Blood oozing (%)	8(18)	5(13)
Active Bleeding (%)	6(14)	7(17)
Therapeutic Intervention		
Epinephrine injection alone (%)	29(66)	28(68)
Epinephrine + APC (%)	14(32)	12(29.5)
Epinephrine + endoclips (%)	1(2)	1(2.5)

Five patients in PO-OMP group and 4 in the IV-OMP group re-bled (11.4% vs 9.8: p=0.810) (Table 2). From the 5 re-bleeding cases in PO-OMP group, 3 re-bled during hospital stay and were successfully managed by endoscopic epinephrine injection. In 2 patients, bleeding developed in 2 weeks after discharge from hospital. They were managed again with epinephrine injection and bleeding did not

reoccur up to 2 weeks after the follow up.

Table 2: Primary and secondary end points.

P value	PO-OMP group (n=44)	IV-OMP group (n=41)	
Re-bleeding (%)	5(11.4)	4(9.8)	0.810
Surgery (%)	0(0)	0(0)	N.S.
Death (%)	1(2)	1(2)	N.S.
Hospital stay (Day)	3.1	3.6	0.130
Blood transfusion (%)	31(71)	33(81)	0.284
Amount of Blood			
Transfusion (Bags)	1.82	1.95	0.641
Re-endoscopy (%)	18(41)	24(59)	0.104

N.S: statistically not significant

In IV-OMP group, 4 patients re-bled, two of them occurred in hospital course and stopped with epinephrine injection and recovered uneventfully. The two other re-bled in follow up period and bleeding stopped with sclerotherapy. Bleeding did not re-occur up to 2 weeks but in one patient 3 weeks later, bleeding re-occurred (5 weeks after index bleeding). Surgical intervention was done in this case. One patient in each group died which was due to a co-morbid disease and not bleeding. The number of blood transfusions and hospital stay were not statistically different in both groups (Table 2). The mean of the hospital stay in both groups was not statistically different (Table 2).

DISCUSSION

Endoscopic therapy decreases but does not eliminates the risk of adverse outcome in peptic ulcer bleeding.[5,6] In recent years, several studies have shown the efficacy of IV PPIs in reducing the adverse outcome of peptic ulcer bleeding, however, despite the optimal dose, the best route of administration has remained controversial.[11,12,23] IV administration of PPIs are expensive, require a dedicated IV line, need nursing supervision and hospital admission. So, it would be reasonable to prescribe oral PPIs to patients with high risk bleeding ulcers provided that it is as effective as its IV counterpart.

Oral PPIs have a high bioavailability. Its effect initiates one hour after ingestion and the maximal plasma concentration is achieved after 2-3 hours.[21] Several studies have shown similar effectiveness of oral and IV PPIs on raising intragastric pH. Laine et al. have shown that intra-gastric pH differs only at the first hour of administration and at 1.5 hour, there is no difference among all hourly intra-gastric pH between both oral and IV lansoprazole.[19] More recently, Javid et al. have demonstrated that IV and high PO doses of various PPIs were equal in their ability to suppress gastric acid secretion and there was no significant difference among various PPIs given through different routes on raising gastric pH above 6 for 72 hours after successful endoscopic haemostasis.[21]

Bardou *et al.* in their meta-analysis have concluded that high dose oral PPI following endoscopic treatment significantly decreased re-bleeding as compared with placebo.[10] Andriulli et al. showed that PPI decreased the adverse outcome of ulcer bleeding independent of the route and dose of PPI.[22] Moreover, Leontiadis et al. recently showed oral PPI both before and after endoscopic haemostatic therapy is likely to be the most cost-effective strategy.[15] Tsai et al. in randomized control head to head trial comparing oral rabeprazole and IV omeprazole, concluded that both prevented re-bleeding equally in high risk peptic ulcers.[18] However, study compared high dose of oral PPI with regular dose of IV PPI (40mg IV infusion each 12 hours).

Our study has several limitations. First we administered the drugs on admission and before the endoscopic therapy. Currently evidence has shown that this downstage the severity of the endoscopic signs of recent bleeding and may reduce the requirement for endoscopic therapy.[19,23] Second, we did not calculate the Rockall score to determine if both groups have equal risk of re-bleeding. Third, we imposed strict exclusion criteria so a large number of patients were dropped, resulting in a very select group.

CONCLUSION

Our study demonstrated that oral high dose PPI was as effective as IV high dose PPI in reducing re-bleeding rate, mortality, hospital stay, and blood transfusion after endoscopic therapy of patients who bleed from peptic ulcers. It may be possible to be

replace IV PPI with PO PPI, although further similar studies are recommended to support the result of this study.

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